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(54) Title: LAMININ 2 AND METHODS FOR ITS USE (54) Titre: LAMININE 2 ET SES METHODES D'UTILISATION (57) Abstract <p>The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.</p> (57) Abrégé <p>La présente invention concerne une laminine 2 sensiblement purifiée, des méthodes de construction d'une laminine 2 de recombinaison, des cellules exprimant ladite laminine 2 de recombinaison, ainsi que des méthodes d'utilisation de la laminine 2 sensiblement purifiée visant à accélérer la régénération des nerfs du système nerveux périphérique et à favoriser la fixation et la migration cellulaires.</p>		

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<p>(54) Title: LAMININ 2 AND METHODS FOR ITS USE (57) Abstract The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.</p>		

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Description

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LAMININ 2 AND METHODS FOR ITS USE**Cross Reference**

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This application claims priority to U.S. Provisional Patent Application Serial Nos. 60/131,720 filed April 30, 1999; 60/139,198 filed June 15, 1999; and 60/143,289 filed July 12, 1999; 60/155,945 filed September 24, 1999; all of which are incorporated herein by reference in their entirety.

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Field of the Invention

This application relates to recombinant laminin 5 and methods for its use.

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Background of the Invention

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Basal laminae (basement membranes) are sheet-like, cell-associated extracellular matrices that play a central role in cell growth, tissue development, and tissue maintenance. They are present in virtually all tissues, and appear in the earliest stages of embryonic development.

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Basal laminae are central to a variety of architectural and cell-interactive functions (See for example, Malinda and Kleinman, *Int. J. Biochem. Cell Biol.* 28:957-959 (1996); Aumailley and Krieg, *J. Invest. Dermatology* 106:209-214 (1996)). For example:

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1. They serve as architectural supports for tissues, providing adhesive substrata for cells.
2. They create perm-selective barriers between tissue compartments that impede the migration of cells and passively regulate the exchange of macromolecules. These properties are illustrated by the kidney glomerular basement membrane, which functions as an important filtration structure, creating an effective blood-tissue barrier that is not permeable to most proteins and cells.
3. Basal laminae create highly interactive surfaces that can promote cell migration and cell elongation during embryogenesis and wound repair. Following an injury, they provide a surface upon which cells regenerate to restore normal tissue function.

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5 4. Basal laminae present information encoded in their structure to contacting cells
that is important for differentiation and tissue maintenance. This information is
communicated to the cells through various receptors that include the integrins,
dystroglycan, and cell surface proteoglycans. Signaling is dependent not only on
10 5 the presence of matrix ligands and corresponding receptors that interact with
sufficient affinities, but also on such topographical factors as ligand density in a
three-dimensional matrix "landscape", and on the ability of basal lamina
components to cluster receptors. Because these matrix proteins can be long-lived,
15 basal laminae create a "surface memory" in the basal lamina for resident and
transient cells.
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20 The basal lamina is largely composed of laminin and type IV collagen
heterotrimers that in turn become organized into complex polymeric structures. To date,
six type IV collagen chains and at least twelve laminin subunits have been identified.
15 25 These chains possess shared and unique functions and are expressed with specific
temporal (developmental) and spatial (tissue-site specific) patterns.

Laminins are a family of heterotrimeric glycoproteins that reside primarily in the
basal lamina. They function via binding interactions with neighboring cell receptors,
and by forming laminin networks, and they are important signaling molecules that can
30 20 strongly influence cellular function. Laminins are important in both maintaining
cell/tissue phenotype as well as promoting cell growth and differentiation in tissue repair
and development.

35 Laminins are large, multi-domain proteins, with a common structural
organization. The laminin molecule integrates various matrix and cell interactive
25 functions into one molecule.

40 Laminin molecules are comprised of an α -, β -, and γ -chain subunit joined
together through a coiled-coil domain. Within this structure are identifiable domains
that possess binding activity towards other laminin and basal lamina molecules, and
membrane-bound receptors. Domains VI, IVb, and IVa form globular structures, and
45 30 domains V, IIIb, and IIIa (which contain cysteine-rich EGF-like elements) form rod-like
structures. (Kamiguchi et al., Ann. Rev. Neurosci. 21:97-125 (1998)) Domains I and II
of the three chains participate in the formation of a triple-stranded coiled-coil structure
(the long arm).
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Table 1 shows the individual chains that each laminin type is composed of:

TABLE 1. Known laminin family members

<i>Protein</i>	<i>Chains</i>
Laminin-1	$\alpha 1\beta 1\gamma 1$
Laminin-2	$\alpha 2\beta 1\gamma 1$
Laminin-3	$\alpha 1\beta 2\gamma 1$
Laminin-4	$\alpha 2\beta 2\gamma 1$
Laminin-5	$\alpha 3\beta 3\gamma 2$
Laminin-6	$\alpha 3\beta 1\gamma 1$
Laminin-7	$\alpha 3\beta 2\gamma 1$
Laminin-8	$\alpha 4\beta 1\gamma 1$
Laminin-9	$\alpha 4\beta 2\gamma 1$
Laminin-10	$\alpha 5\beta 1\gamma 1$
Laminin-11	$\alpha 5\beta 2\gamma 1$
Laminin-12	$\alpha 2\beta 1\gamma 3$

Four structurally-defined family groups of laminins have been identified. The first group of five identified laminin molecules all share the $\beta 1$ and $\gamma 1$ chains, and vary by their α -chain composition ($\alpha 1$ to $\alpha 5$ chain). The second group of five identified laminin molecules all share the $\beta 2$ and $\gamma 1$ chain, and again vary by their α -chain composition. The third group of identified laminin molecules has one identified member, laminin 5, with a chain composition of $\alpha 3\beta 3\gamma 2$. The fourth group of identified laminin molecules has one identified member, laminin 12, with the newly identified $\gamma 3$ chain ($\alpha 2\beta 1\gamma 3$).

Some progress has been made in elucidating the relationship between domain structure and function. (See, for example, Wewer and Engvall, *Neuromusc. Disord.* 6:409-418 (1996).) The overall sequence similarity among the homologous domains in different chains varies, but it is highest in domain VI (thought to play a key role in laminin polymerization), followed by domains V (possibly involved in protein-protein interactions) and III (entactin/nidogen binding; possible cell adhesion sites), and is lowest in domains I, II (both thought to be involved in intermolecular assembly, and containing possible cell adhesion sites), and G. Not all domains are present in all 3 types of chains. The globular G domain (thought to be involved in cell receptor binding) is present only in the α chains. Other domains may not be present in all chains within a certain chain type. For example, domain VI is absent from $\alpha 3$, $\alpha 4$, and $\gamma 2$ chains. (Wewer and Engvall, 1996)

5 As a result of their large size (>600 kD) and unique structure, laminin molecules
can be resolved in the electron microscope. (Wewer and Engvall, 1996) Typically,
laminins appear as cross-shaped molecules in an electron micrograph. The three short
10 arms of the cross represent the amino terminal portions of each of the three separate
5 laminin chains (one short arm per chain). The long arm of the cross is composed of the
C-terminal parts of the three chains, which together form a coiled coil structure. (Wewer
and Engvall, 1996) The long arm ends with the globular G domain.

15 The coiled-coil domain of the long arm is crucial for assembly of the three chains
of laminin. (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-10194 (1997)). Disulfide
10 bonds bridge and stabilize all three chains in the most proximal region of the long arm
and join the β and γ chains in the most distal region of the long arm.

20 A model of laminin receptor-facilitated self-assembly, based on studies conducted
with cultured skeletal myotubes and Schwann cells, predicts that laminins bind to their
receptors, which freely diffuse in a fluidic membrane when ligand-free. Receptor
15 engagement forces the laminins into a high local two-dimensional concentration,
25 facilitating their mass-action driven assembly into ordered surface polymers. In this
process, the engaged receptors are also reorganized, accompanied by cytoskeletal
rearrangements. (Colognato, J. Cell Biol. 145:619-631 (1999)) This reorganization
30 activates the receptors, causing signal transduction with the alteration of cell expression,
20 shape and/or behavior.

One class of laminin receptors are the integrins, which are cell surface receptors
that mediate many cell-matrix and cell-cell interactions. Integrins are heterodimers,
35 consisting of an α and a β subunit. 16 α - and 8 β -subunits are known, and at least 22
combinations of α and β subunits have been identified to date. Some integrins have only
25 one or a few known ligands, whereas others appear to be very promiscuous. Binding to
40 integrins is generally of low affinity, and is dependent on divalent cations. Integrins,
activated through binding to their ligands, transduce signals via kinase activation
cascades, such as focal adhesion and mitogen-activated kinases. Several different
45 integrins bind different laminin isoforms more or less specifically. (Aumailley et al., In
30 The Laminins, Timpl and Ekblom, eds., Harwood Academic Publishers, Amsterdam.
pp. 127-158 (1996))

5 Laminin 2 is composed of $\alpha 2$ (400 kD), $\beta 1$ (approximately 100 kD), and $\gamma 1$ (approximately 100 kD) chains. The C-terminal G domain of the $\alpha 2$ chain forms a large globular structure responsible for binding to α -dystroglycan. (Kamiguchi et al., 1998).

10 The short arm domains of laminin 1 are involved in the self-aggregation process (Schittney and Yurchenco, J. Cell Biol. 110:825-832 (1990)) and with extracellular matrix components, such as type IV collagen. Homology between the $\alpha 1$ (laminin 1) and $\alpha 2$ chains is 58.6%. The significant homology between the $\alpha 1$ and $\alpha 2$ chains, especially in the N-terminal domains, and their identical β and γ chains, suggest that laminin 2 has a similar structural organization to laminin 1. (Kamiguchi et al., 1998)

15 Laminin 2 was originally found in the basement membranes of the placenta, striated muscle, and Schwann cells. (Leivo and Engvall, Proc. Natl. Acad. Sci. USA 85:1544-1548 (1998)) In normal adults, laminin 2 is predominant in the basal lamina of skeletal muscle, where it serves to provide mechanical reinforcement to the sarcolemma by linking the extracellular matrix and the subsarcolemmal cytoskeleton. (Sanes et al., J. Cell Biol. 111:1685-1699 (1990))

20 Genetic defects affecting the structure or expression of laminin 2 are the causes of a major type of congenital muscular dystrophy (CMD). Laminin 2 has been shown to be specifically required for stabilizing myotubes during skeletal muscle development, and for preventing apoptosis, which is believed to explain some of the pathological events observed in CMD. (Kamiguchi et al., 1998)

25 In vitro studies have demonstrated that partially purified laminin 2 is important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin $\alpha 2$ chain restoration in a laminin $\alpha 2$ deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197)

30 Laminin 2 is also the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote Schwann cell migration, neurite outgrowth, and neurite regeneration (Kamiguchi et al., 1998), as well as myelin formation by oligodendrocytes (Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999)). The results of various experiments have indicated that laminin 2, rather than laminin 1, is important in Schwann cell/basal lamina interactions, especially at early developmental stages. (Kamiguchi et al., 1998) Other

5 studies have demonstrated that partially purified laminin 2 promotes neuronal cell migration and axon outgrowth (Agius and Cochard, J. Neurosci. 18:328-338 (1998); Kamiguchi et al., 1998; U.S. Patent Nos. 5,444,158; 5,872,231; 5,624,905; and 5,863,743; Bates and Meyer, Develop. Biol. 181:91-101 (1997)). In a laminin 2
10 5 deficient CMD animal model, CMD was accompanied by dysmyelination of peripheral motor nerves, indicating that laminin 2 plays an important role in peripheral myelinogenesis.

15 Partially purified laminin 2 has also been shown to promote cell migration and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796
20 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

25 It has also been demonstrated that the molecular basis of the neural tropism of *Mycobacterium leprae* is attributable to the specific binding of *M. leprae* to the G domain of the laminin $\alpha 2$ chain on Schwann cell-axon units, while α -dystroglycan
30 (α DG) was shown to serve as a Schwann cell receptor for *M. leprae*. (Rambukkana et al., Science 282:2076-2079 (1998); Rambukkana et al., Cell 88:811-821 (1997)). Native α DG was shown to competitively inhibit the laminin-2 mediated *M. leprae* binding to primary Schwann cells. (Rambukkana et al. 1998)

35 Thus, research and therapeutic applications for laminin 2 and fragments thereof include, but are not limited to, peripheral nervous system (PNS) nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical
40 devices, improving the "take" of grafts, and preparing improved cell culture devices and media.

45 25 At present, there is not a means to isolate adequate substantially purified laminin 2 from cell or tissue sources for research or therapeutic purposes, nor has a means been developed for production of recombinant heterotrimeric laminin 2. Laminin 2 can be partially purified from either placenta, or, in lesser amounts, from skeletal muscle. Human placenta has provided the only source for obtaining up to several milligrams of protein.
50 30 (Cheng et al., J. Biol. Chem. 272:31525-32, 1997) However preparations of this laminin normally contain about an equal molar quantity of laminin 4 ($\alpha 2\beta 2\gamma 1$) and the protein nidogen (entactin). The nidogen is bound to the laminin through a fairly strong but non-covalent association. It is difficult to remove most of the laminin 4, and even after

5 additional steps, a significant contaminating level of laminin 4 remains. Denaturing conditions are required to remove the nidogen.

Therefore, there is a need in the art for adequate amounts of substantially purified laminin-2, and methods for making laminin 2. A preferred method of production is the
10 5 use of recombinant DNA technology to engineer a cell line of choice to produce recombinant laminin-2. A recombinant-based method of laminin-2 production has several advantages over purification from tissue or isolation from cell lines in culture:

1. The recombinantly produced protein is free of pathogens. While this is also
15 true for endogenous cell culture produced protein, protein derived from human tissue carries a risk for contamination by HIV, hepatitis, and other infectious agents.

2. Expression levels of the protein, and hence yields, can be improved
20 through the use of genetically engineered genes/vectors that enhance the production of the encoded protein.

3. It is possible to engineer additional peptide sequences to the protein chain
15 that provides a binding site for a commercially viable affinity purification procedure.

4. The method can provide for the modification of protein structure/function
25 through the addition, substitution, elimination, and/or other modifications of protein domain structures. For example, it may be desirable to introduce an integrin binding site (e.g. RGD), switch integrin recognition sites, or engineer in a stable binding site to a
30 synthetic substrate. Thus, the creation of expression vectors that express laminin chains generates enormous flexibility for future uses and creates a basis for creating second generation "designer" laminins.
35

25 Summary of the Invention

40 The present invention fulfills the need in the art for substantially purified laminin 2 protein, methods for making substantially purified recombinant laminin 2 (hereinafter referred to as r-laminin 2), and methods of using substantially purified laminin 2 for
30 research and therapeutic purposes including, but not limited to, peripheral nerve regeneration, treatment of degenerative muscle disorders, angiogenesis regulation, promoting cell attachment and migration, ex vivo cell therapy, improving the "take" of
45

5 grafts, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media

10 In one aspect, the present invention provides mammalian cells that have been transfected with expression vector(s) encoding at least one of the laminin $\alpha 2$, $\beta 1$ and $\gamma 1$ chains, wherein the cells secrete r-laminin 2.

15 In another aspect, the present invention provides substantially purified laminin 2 and methods for producing r-laminin 2.

20 In a further embodiment, the present invention provides a novel, isolated laminin 2 $\alpha 2$ nucleic acid and $\alpha 2$ protein. In this embodiment, the protein product contains an additional 30 amino acids at its carboxyl terminus relative to the previously reported sequence.

25 In a further aspect, the present invention provides pharmaceutical compositions, comprising substantially purified laminin 2, or the novel recombinant $\alpha 2$ protein together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions can optionally be provided with other compounds, such as extracellular matrix components.

30 The present invention further provides methods for peripheral nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the substantially purified laminin 2, or pharmaceutical compositions thereof, for the desired outcome.

35 In a further aspect, the present invention provides improved medical devices or grafts, wherein the improvement comprises applying to the devices or grafts an amount effective of substantially purified laminin 2 or pharmaceutical compositions thereof, for the desired application. Such devices can optionally be provided with other compounds, such as extracellular matrix components to further improve the biocompatibility or the effectiveness of the medical device or graft.

40 In a further aspect, the invention provides improved cell culture devices, by providing an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, for the attachment of cells to a cell culture device for the subsequent proliferation/differentiation/stasis of the cells.

45 In another aspect, the invention provides a cell culture growth supplement, comprising substantially purified laminin 2. In another aspect, the invention provides an

improved cell culture growth media, wherein the improvement comprises the addition of substantially purified laminin 2 to the growth medium.

Brief Description of the Figures

- Figure 1** is a photograph of an Coomassie blue-stained SDS-polyacrylamide gel of recombinant laminin 2 compared to laminin 1.
- Figure 2** is an electron micrographs of purified recombinant laminin 2.
- Figure 3** is an immunoblot demonstrating the co-polymerization of laminin 2.
- Figure 4** is a graph demonstrating C2C12 myoblast adherence to recombinant laminin 2.
- Figure 5** shows the correct sequence of the laminin $\alpha 2$ cDNA and deduced amino acid sequence.

Detailed Description of the Preferred Embodiments

All references, patents and patent applications are hereby incorporated by reference in their entirety.

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutscher, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

As used herein, "laminin 2" includes both r-laminin 2 and laminin 2 substantially purified from tissue sources.

As used herein, the term "r-laminin 2" refers to recombinant laminin 2, expressed by a cell that has been transfected with one or more expression vectors comprising at least one nucleic acid sequence encoding a laminin 2 chain selected from the $\alpha 2$, $\beta 1$ and $\gamma 1$ chains, processed forms thereof, or other portions thereof that are capable of forming a

heterotrimeric laminin 2 and maintaining laminin 2 activity. Such r-laminin 2 can thus comprise $\alpha 2$, $\beta 1$, and $\gamma 1$ sequences from a single organism, or from different organisms. Laminin 2 chain DNA sequences and their encoded proteins from a variety of organisms are known in the art. (See, for example, Vuolteenaho et al., J. Biol. Chem. 265:15611-15616 (1990); Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkariainen et al., J. Biol. Chem. 263:6751-6758 (1988); Sasaki and Yamada, J. Biol. Chem. 262:17111-17117 (1987); Sasaki et al., Proc. Natl. Acad. Sci. 84:935-939 (1987); Pikkariainen et al., J. Biol. Chem. 262:10454-10462 (1987); and Bernier et al., Matrix Biol. 14:447-455 (1995), all references incorporated by reference herein in their entirety).

The invention encompasses those laminin molecules wherein one or two of the chains that make up the recombinant heterotrimeric laminin 2 are encoded by endogenous laminin 2 chains. In a preferred embodiment, r-laminin 2 is produced by cells that are transfected with one or more expression vectors comprising nucleic acid sequences encoding each of mammalian $\alpha 2$, $\beta 1$ and $\gamma 1$ chains, processed forms thereof, or other portions thereof that are capable of forming a heterotrimeric laminin 2 and maintaining laminin 2 activity.

In the present invention, laminin 2 is a secreted protein, which is capable of being directed to the ER, secretory vesicles, and the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Such processing event can be variable, and thus may yield different versions of the final "mature protein". The substantially purified laminin 2 of the present invention includes heterotrimers comprising both the full length and any such processed laminin 2 chains.

As used herein, the term "substantially purified" means that the laminin 2 so designated has been separated from its in vivo cellular environment.

As used herein, a laminin 2 polypeptide chain refers to a polypeptide chain according to one or more of the following:

(a) comprises a polypeptide structure selected from the group consisting of:

1. R1-R2-R3
2. R1-R2-R3(e)
3. R3

4. R3(e)
5. R1-R3
6. R1-R3(e)
7. R2-R3
8. R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or an artificial sequence; R3 is a secreted laminin chain selected from $\alpha 2$, $\beta 1$, and $\gamma 1$ chains; and R3(c) is a secreted laminin chain selected from the $\alpha 2$, $\beta 1$, and $\gamma 1$ chains that further comprises an epitope tag (such as those described below), which can be placed at any position within the laminin chain amino acid sequence; and/or

(b) is encoded by a polynucleotide that is substantially similar to on or more of the disclosed laminin chain polynucleotide sequences (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31) or fragments thereof; and/or

(c) is encoded by a polynucleotide that hybridizes under high or low stringency conditions to coding regions, or portions thereof, of one or more of the recombinant laminin 2 chain DNA sequences disclosed herein (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31) fragments thereof, or complementary sequences thereof; and/or

(d) has at least 70% identity to one or more of the disclosed laminin 2 polypeptide chain amino acid sequences (SEQ ID NOS.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or fragments thereof), preferably at least 80% identity, and most preferably at least about 90% identity.

The phrase "substantially similar" is used herein in reference to polynucleotide or polypeptide sequences having one or more conservative variations from the laminin 2 sequences disclosed herein, including but not limited to deletions, insertions, inversions, repeats, and substitutions, wherein the resulting laminin chain is functionally equivalent to those disclosed herein.

For example, conservative polynucleotide variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the amino acid sequence of the encoded polypeptide. Nucleotide variants

5 produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, including but not limited to optimizing codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

10 Naturally occurring conservative variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring conservative variants may be produced by mutagenesis techniques or by direct synthesis.

20 Using known methods of protein engineering and recombinant DNA technology, conservative polynucleotide variants may be generated to improve or alter the characteristics of the expressed laminin chain polypeptides. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein. (See, for example, Ron et al., J. Biol. Chem. 268: 2984-2988 (1993); Dobeli et al., J. Biotechnology 7:199-216 (1988)) Ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. (See, for example, Gayle et al., J. Biol. Chem 268:22105-22111 (1993)) Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained.

35 Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

40 The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

5 The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

10 As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

15 Besides conservative amino acid substitution, "substantially similar" polypeptides of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be "substantially similar" according to the present invention.

20 For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

5 "Stringency of hybridization" is used herein to refer to conditions under which nucleic acid hybrids are stable. The invention also includes nucleic acids that hybridize under high stringency conditions (as defined herein) to all or a portion of the coding sequences of the laminin chain polynucleotides disclosed herein, or their complements.

10 5 The hybridizing portion of the hybridizing nucleic acids is typically at least 50 nucleotides in length. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T_M) of the hybrids. T_M decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is
15 performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20
20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are laminin 2-encoding nucleic acid sequences that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily
30 accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4 ; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes
35 at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in
45 hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.
50

5 As used herein, "percent identity" of two amino acids or of two nucleic acids is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST
10 programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3, to obtain an amino acid sequence homologous to a polypeptide of the
15 invention. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids. Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used. See <http://www.ncbi.nlm.nih.gov>.

Further embodiments of the present invention include polynucleotides encoding
20 laminin 2 chain polypeptides having at least 70% identity, preferably at least 80% identity, and most preferably at least 90% identity to one or more polypeptide sequence contained in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or fragments thereof.

30 As used herein, " α 2 polynucleotide" refers to a polynucleotide encoding an α 2 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid sequence substantially similar to one or more of the amino acid sequences set forth in
35 SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably 80% identity, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID
40 NO: 2, 4, 6, 8, 10, 12, or fragments thereof; (c) the α 2 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 1, 3, 5, 7, 9, 11, fragments thereof, or complementary sequences thereof; or (d) the
45 α 2 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted α 2 chain polypeptides.

5 As used herein, "β1 polynucleotide" refers to polynucleotides encoding a β1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode a polypeptide substantially similar to one or more of the amino acid sequences set forth in
10 SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (c) the β1 cDNAs hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 13,
15 15, 17, 19, fragments thereof, or complementary sequences thereof; or (d) the β1 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(c); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted β1 chain polypeptides.

25 As used herein, "γ1 polynucleotide" refers to polynucleotides encoding a γ1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid that is substantially similar to one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (b) polynucleotides that encode polypeptides
30 which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (c) the γ1 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, fragments thereof, or complementary sequences thereof; or (d) the γ1
35 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted γ1 chain polypeptides.

45 As used herein, the term "epitope tag" refers to a polypeptide sequence that is expressed as part of a chimeric protein, where the epitope tag serves as a recognition site for binding of antibodies generated against the epitope tag, or for binding of other
50 molecules that can be used for affinity purification of sequences containing the tag.

5 As used herein, the term "increased biocompatibility" refers to reduced induction of acute or chronic inflammatory response, and reduced disruption of the proper differentiation of implant-surrounding tissues for laminin 2-coated biomaterials relative to an analogous, non-coated biomaterial.

10 5 In one aspect, the present invention provides r-laminin 2 expressing-cells that have been transfected with an expression vector containing promoter sequences that are operatively linked to nucleic acid sequences encoding at least one polypeptide sequence comprising the $\alpha 2$, $\beta 1$ and $\gamma 1$ chains of laminin 2, or fragments thereof, wherein the
15 transfected cells secrete heterotrimeric laminin 2 containing the recombinant laminin chain. In a preferred embodiment, the cells are transfected with recombinant expression vectors containing promoter sequences that are operatively linked to nucleic acid
20 sequences encoding polypeptide sequences comprising each of the mammalian $\alpha 2$, $\beta 1$ and $\gamma 1$ chains of laminin 2, or fragments thereof. After the transfection(s), the cells express each of the recombinant laminin 2 chains, which form the heterotrimer, before r-laminin 2
25 secretion into the media.

25 In a preferred embodiment, cDNAs encoding $\alpha 2$, $\beta 1$ and $\gamma 1$ laminin chains, or fragments thereof, are subcloned into an expression vector. Alternatively, laminin 2 $\alpha 2$, $\beta 1$ and/or $\gamma 1$ genomic sequences, including one or more introns, can be used.

30 Any cell capable of expressing and secreting the r-laminin 2 can be used. Preferably, eukaryotic cells are used, and most preferably mammalian cells are used, including but not limited to kidney and epithelial cell lines. In a most preferred
35 embodiment, the mammalian cells do not express all of the laminin 2 chains endogenously. Carbohydrate and disulfide post-translational modifications are believed to be required for laminin 2 protein folding and function. This makes the use of eukaryotic
25 cells preferable for producing functional r-laminin 2, although other systems are useful for obtaining, for example, antigens for antibody production.

40 "Recombinant expression vector" includes vectors that operatively link a nucleic acid coding region or gene to any promoter capable of effecting expression of the gene product. The promoter sequence used to drive expression of the individual chains or r-
45 laminin 2 may be constitutive (driven by any of a variety of promoters, including but not limited to, CMV, SV40, RSV, actin, EF) or inducible (driven by any of a number of inducible promoters including, but not limited to, tetracycline, ecdysone, steroid-
50

responsive). The expression vector must be replicable in the host organisms either as an episome or by integration into host chromosomal DNA. In a preferred embodiment, the expression vector comprises a plasmid. However, the invention is intended to include other expression vectors that serve equivalent functions, such as viruses.

In one embodiment, at least one of the laminin chain polynucleotide sequences, or fragments thereof, is operatively linked to a nucleic acid sequence encoding an "epitope tag", so that at least one of the chains is expressed as a fusion protein with an expressed epitope tag. The epitope tag may be expressed as the amino terminus, the carboxy terminus, or internal to any of the polypeptide chains comprising r-laminin 2, so long as the resulting r-laminin 2 remains functional. Any epitope tag may be utilized, so long as it can be used as the basis for affinity purification of the resulting r-laminin 2. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Mannheim Biochemicals).

In another embodiment, one of the r-laminin 2 chains is expressed as a fusion protein with a first epitope tag, and at least one other r-laminin chain is expressed as a fusion protein with a second epitope tag. This simplifies the purification procedure and facilitates higher recoveries. Alternatively, the same epitope tag can be used to create fusion proteins with more than one of the r-laminin chains.

In a further embodiment, the epitope tag can be engineered to be cleaveable from the r-laminin 2 chain(s). Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using antibodies against laminin 2 antibodies or other laminin 2 binding molecules.

Transfection of the expression vectors into eukaryotic cells can be accomplished via any technique known in the art, including but not limited to calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Transfection of bacterial cells can be done by standard methods.

In a preferred embodiment, the cells are stably transfected. Methods for stable transfection and selection of appropriate transfected cells are known in the art. In a most preferred embodiment, a CMV promoter driven expression vector is used in a human kidney embryonic 293 cell line.

5 In one example, media from cells transfected with a single laminin chain are initially analyzed on Western blots using laminin chain-specific antibodies. The expression of single laminin chains following transfection is generally intracellular. Clones showing reactivity against individual transfected chain(s) are verified by any
10 appropriate method, such as PCR, reverse transcription-PCR, or nucleic acid hybridization, to confirm incorporation of the transfected gene. Preferably, analysis of genomic DNA preparations from such clones is done by PCR using laminin chain-specific primer pairs. Media from transfected clones producing all three chains are further analyzed
15 for r-laminin 2 secretion and/or activity, by any appropriate method, including Western blot analysis and cell binding assays. Activity of the r-laminin 2 is preferably analyzed in cell adhesion and protein binding assays.

20 In another aspect, the present invention provides substantially purified laminin 2, preferably r-laminin 2. In one embodiment, the substantially purified laminin 2 comprises a first chain comprising an $\alpha 2$ chain polypeptide; a second chain comprising a $\beta 1$ chain polypeptide; and a third chain comprising a $\gamma 1$ chain polypeptide. Alternatively, the r-laminin 2 comprises a first chain that is substantially similar to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; a second chain that is substantially similar to at least one of the sequence shown in SEQ ID NO: 12, 14, 16, or 18, or fragments thereof; and a third chain that is substantially similar to the
25 sequence shown in SEQ ID NO: 20, 22, 24, or 26, or fragments thereof.

30 In another embodiment, the substantially purified r-laminin 2 comprises a first chain comprising a polypeptide that is at least about 70% identical to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, or 10, or fragments thereof; a second chain comprising a polypeptide that is at least 70% identical to at least one of the sequences
35 shown in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; and a third chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof, wherein the first, second, and third polypeptides assemble into a recombinant heterotrimeric laminin 2.

40 It is preferred that at least one of the first, second, or third chains of the substantially purified human r-laminin 2 is expressed as a fusion protein with an epitope tag.
45

50 Alternatively, the r-laminin 2 comprises a heterotrimeric polypeptide structure, wherein each individual chain comprises a general structure selected from the group

consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted $\alpha 2$, $\beta 1$, or $\gamma 1$ laminin chain; and R3(e) is a secreted laminin $\alpha 2$, $\beta 1$, and $\gamma 1$ chain that further comprises an epitope tag (such as those described above), which can be placed at any position within the laminin chain amino acid sequence.

In a preferred embodiment, purification of the r-laminin 2 is accomplished by passing media from the transfected cells through an affinity column. For example, antibodies or other binding molecules that bind to a peptide epitope expressed on at least one of the recombinant chains are attached to an affinity column, and bind r-laminin 2 that has been secreted into the media. The r-laminin 2 is removed from the column by passing excess peptide through the column. The eluted protein can subsequently be further purified, if desired.

Eluted fractions are analyzed by any appropriate method, including gel electrophoresis and Western blot analysis. In a further embodiment, the peptide epitope can be cleaved after purification. In other embodiments, two or three separate r-laminin chains are expressed as fusion proteins, each with a different epitope tag, permitting two or three rounds of purification and a doubly or triply purified r-laminin 2. The epitope tag can be engineered so as to be cleavable from the r-laminin 2 chain(s) after purification. Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using laminin 2 specific antibodies or other laminin 2 binding molecules.

In another aspect, the present invention provides a novel polynucleotide encoding the laminin $\alpha 2$ chain, consisting of the sequence shown in SEQ ID NO:1. In another aspect, the present invention provides a novel laminin 2 α polypeptide chain, consisting of the sequence shown in SEQ ID NO:2. These sequences differ from the previously reported sequences, in that the laminin $\alpha 2$ -chain encoding nucleic acid consists of an extra nucleotide, resulting in the nucleic acid encoding an additional 30 amino acids at the C-terminus over what has previously been reported.

5 The present invention further provides pharmaceutical compositions comprising substantially purified laminin 2, and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition comprises substantially purified r-laminin 2. According to this aspect of the invention, other agents can be included in the
10 5 pharmaceutical compositions, depending on the condition being treated. The pharmaceutical composition may further comprise one or more other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, integrins, α -dystroglycan, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans,
15 10 epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or nerve growth factors, and peptide fragments thereof. In an alternative embodiment, the pharmaceutical compositions comprise the novel laminin α 2 polypeptide chain of the invention together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations comprising substantially purified laminin 2 can be
15 25 prepared in any suitable form, and generally comprise the substantially purified laminin 2 in combination with any of the well known pharmaceutically acceptable carriers. The carriers can be injectable carriers, topical carriers, transdermal carriers, and the like. The preparation may advantageously be in a form for topical administration, such as an ointment, gel, cream, spray, dispersion, suspension or paste. The preparations may further
30 20 advantageously include preservatives, antibacterials, antifungals, antioxidants, osmotic agents, and similar materials in composition and quantity as is conventional. Suitable solutions for use in accordance with the invention are sterile, are not harmful for the proposed application, and may be subjected to conventional pharmaceutical operations
35 25 such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. For assistance in formulating the compositions of the present invention, one may refer to Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa. (1975).

In further aspect, the present invention provides methods and kits for peripheral
45 30 nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the

5 substantially purified laminin 2, or pharmaceutical compositions thereof for the desired outcome. In all of these methods, the use of r-laminin 2 is preferred.

As used herein, the term "grafts" refers to both natural and prosthetic grafts as well as implants.

10 5 The treatment of peripheral nerve injuries is a common surgical problem. Nerve injuries can result from trauma, chronic compression, ischemia, radiation, errors of therapy and other causes. The severe forms of injury, in which the nerve is partially or completely disrupted, are difficult or impossible to treat by existing therapies. The basal lamina plays
15 a key role in providing a migration guide for regenerating axons and Schwann cells following such nerve injury. The prognosis for successful regeneration is significantly better if the basement membrane remains intact.

20 Recently, the feasibility of using basal lamina coated bio-materials as a workable graft was demonstrated in a rat model in two studies (Kauppila *et al.*, Exp. Neurol. 123:181-191 (1993); Tong *et al.*, Brain Res. 663:155-162). In the first study, a bovine
25 tendon collagen I graft sheet was impregnated with partially purified, non-recombinant mouse laminin-1, with the cut ends of the rat sciatic nerve (8 mm removed) sutured to the ends of the rolled graft. Function to the affected limb, as judged by electrophysiological and behavioral measurements at 4 months post-operatively, was restored (~60-80%
30 relative to unaffected contralateral nerve) with the laminin graft at a level equivalent to restoring the transected nerve segment. The authors further reported that the laminin graft caused fewer signs of pain. In the second study, the authors created a graft by coating collagen fibrils with purified, non-recombinant laminin and fibronectin, and inserting the
35 modified fibrils in a collagen sleeve. This graft, about 1 cm in length, was again sutured to the proximal and distal end of a transected sciatic nerve. Axonal/Schwann cell growth occurred into the graft with ultimate reattachment with the distal nerve stump. By light
40 and electron microscopy, restoration of essential structural/cellular elements was found in the graft with ultimate resorption of the graft material. The laminin/fibronectin coat was essential since the collagen fibrils alone were not sufficient to restore the nerve.

45 30 The studies of Kauppila *et al.* and Tong *et al.* not only demonstrate the value of basal lamina components in regeneration, but also demonstrate therapeutic feasibility. A similar method for enhancing nerve regeneration using a hollow nerve regeneration conduit coated with type I collagen and purified placental laminin (predominately laminin
50 1) has also been disclosed. (U.S. Patent No. 5,019,087)

Thus, in one embodiment, the present invention provides methods to promote peripheral nerve regeneration, comprising coating a nerve graft with an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, to promote regeneration of the nerve. Laminin 2 is the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote neuronal cell migration and regeneration, axon outgrowth, myelin membrane formation by oligodendrocytes, and Schwann cell migration. (Kamiguchi et al., (1998); Agius and Cochard, J. Neurosci. 18:328-338 (1998); U.S. Patent No. 5,444,158; Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999); Bates and Meyer, Develop. Biol. 181:91-101 (1997)). The present invention provides a plentiful supply of substantially purified laminin 2, or pharmaceutical compositions thereof, for coating nerve grafts, and thereby promoting neuronal and Schwann cell migration, axonal migration, myelin membrane formation, and nerve regeneration. The graft can comprise a nerve graft, or a prosthetic graft. Both bioresorbable and non-resorbable materials have been used in tubes for bridging nerve gaps. (See for example, Nyilas, et al., (Trans. Soc. Biomater., 6, 85, 1983), Molander, et al. (Biomaterials, Vol. 4, pp. 276-280, October, 1983), Colin, et al., (Journal of Dental Research July, 1984, pp. 987-993).

In another embodiment, r-laminin 2 is used to promote the healing of degenerative muscle disorders. Laminin 2 is known to be important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)). In vitro studies have demonstrated that partially purified laminin 2 promotes myoblast fusion and myotube formation. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin $\alpha 2$ chain restoration in a laminin $\alpha 2$ deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197 (1996)) Thus, mammalian cells that express r-laminin 2, or the novel laminin $\alpha 2$ chain of the invention, can be used for cell therapy, to treat patients with degenerative muscle disorders such as muscular dystrophies that are characterized by a laminin $\alpha 2$ deficiency.

Partially purified laminin 2 has also been shown to promote the migration of and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal or mesenchymal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

Thus, in another embodiment, substantially purified laminin 2, or pharmaceutical compositions thereof, can be added to medical devices, tissue culture plates, grafts, and cell culture media to provide important ligand substrates to maintain and expand primary explanted human tissue cells. This takes advantage of what has been observed by many investigators over the past decade, i.e., basal lamina components, in particular laminins, provide optimal surfaces for the adhesion, spreading, propagation, and maintenance of the differentiated phenotype of a large variety of cells. This property of substantially purified laminin 2 can be exploited to increase the biocompatibility of a medical device, to permit the maintenance of human cells in a laboratory affording time to find a suitable donor, and for the expansion of cell populations for transplantation and somatic gene therapy. Possible target cells for *ex vivo* therapy include cells of muscle and neuronal origin, lymphocytes and cells of the immune system, pancreatic islet, parathyroid, adrenal, pituitary, hepatic, cardiac muscle and stem cells.

In another embodiment, the present invention provides methods for regenerating cells and tissues both *in vivo* and *ex vivo*. Many of the current approaches for tissue engineering begin with a collagen/polymer scaffolding that is seeded with appropriate cells that can proliferate and differentiate into cell masses and tissue sub-structures. In the development of these methods, attempts have been made to add coatings to the scaffolding to provide for a more natural surface for cell interactions, with the expectation that cell proliferation and tissue development would be enhanced. Coating these matrices with the substantially purified laminin 2 provides for a natural ligand interactive surface to promote normal cell adherence, cell growth and tissue development. Thus, the availability of substantially purified laminin 2 is expected to significantly improve tissue regeneration procedures.

Laminins, or cell extracts containing laminins, have been shown to regulate angiogenesis in a biphasic manner. (See, for example, Nicosia et al., *Dev. Biol.* 164:197-206 (1994); Bonfil et al., *Int. J. Cancer* 58:233-239 (1994)). At lower concentrations (30-300 $\mu\text{g/ml}$), a laminin-entactin complex stimulated angiogenesis in a three-dimensional culture, while at 3000 $\mu\text{g/ml}$ the same complex was inhibitory to angiogenesis. Thus, in another aspect, the present invention provides methods for regulating angiogenesis, comprising contacting a tissue or culture substrate with an amount effective of laminin 2 or pharmaceutical compositions thereof to regulate angiogenesis. In one embodiment, the laminin 2 is used to promote angiogenesis by contacting a tissue or culture substrate with

5 an amount effective of laminin 2 to promote angiogenesis. In another embodiment, the laminin 2 is used to inhibit angiogenesis, by contacting the tissue or culture substrate with an amount effective of laminin 2 to inhibit angiogenesis. An example of culture substrates to be contacted with laminin 2 to regulate angiogenesis are those used for tissue engineering purposes.

10 In a further aspect, the present invention comprises medical devices with improved biocompatibility, wherein the devices are coated with the substantially purified laminin 2, or pharmaceutical compositions thereof, alone or in combination with other proteins or agents that serve to increase the biocompatibility of the device surface. The coated device stimulates cell attachment and provides for diminished inflammation and/or infection at the site of entry of the appliance.

20 Preferably, the device is made of or coated with a biocompatible metal that may be either stainless steel or titanium. Alternatively, the device is made of or coated with a ceramic material, or a polymer including but not limited to polyester, polyglycolic acid or a polygalactose-polyglycolic acid copolymer.

25 One particular use of the present invention is to increase neuronal, skeletal muscle, endothelial or mesenchymal cell adhesion to target surfaces. For example, vascular grafts and stents may be coated with substantially purified laminin 2 to stimulate endothelial cell attachment, and to minimize platelet adhesion to the graft or stent surface. Alternatively, bone or connective tissue grafts or prostheses may be coated with substantially purified laminin 2 to stimulate adhesion of the appropriate cell type and improved efficiency of grafting.

35 If the device is made of a natural or synthetic biodegradable material in the form of a mesh, sheet or fabric, substantially purified laminin 2 may be applied directly to the surface thereof. Appropriate cells may then be cultured on the matrix to form transplantable or implantable devices, including dental abutment pieces, needles, metal pins or rods, indwelling catheters, colostomy tubes, surgical meshes and any other appliance for which coating with the substantially purified laminin 2 is desirable. Alternatively, the devices may be implanted and cells may be permitted to attach in vivo.

40 45 30 Coupling of the substantially purified laminin 2 may be non-covalent (such as by adsorption), or by covalent means. The device may be immersed in, incubated in, or sprayed with substantially purified laminin 2 or pharmaceutical compositions thereof.

50 The dosage regimen for various treatments using the substantially purified laminin

5 2 of the present invention is based on a variety of factors, including the type of injury or condition, the age, weight, sex, medical condition of the individual, the severity of the condition, and the route of administration. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods. Laminins are
10 5 extremely potent molecules, and one or a few molecules per cell could produce an effect. Thus, effective doses in the pico-gram per milliliter range are possible if the delivery is optimized. Laminins are sometimes present in an insoluble form in the basement membrane and have the capability of polymerizing at concentrations as low as about 50
15 $\mu\text{g/ml}$, depending on the laminin isoform and the conditions. Laminins can also polymerize into a gel at a concentration of 2-3 mg/ml . Dosage levels of the order of
20 between 1 ng/ml and 10 mg/ml are thus useful for all methods disclosed herein, preferably between about 1 $\mu\text{g/ml}$ and about 3 mg/ml .

The present invention also provides a method for inducing cell attachment to the device (as disclosed above), comprising coating the appliance with substantially purified
25 15 laminin 2 prior to incubation with cells appropriate for the desired application.

In another aspect of the present invention, substantially purified laminin 2 is used for the culture of cells, including but not limited to neuronal, skeletal muscle, fibroblasts, Schwann cells, cells of mesenchymal origin, and endothelial cells, by contacting the cells
30 with an amount effective of substantially purified laminin 2 to stimulate attachment and proliferation/differentiation/stasis of cells. The substantially purified laminin 2 can either be provided in the cell culture medium, or as a cell culture medium supplement, or may be coated on the surface of a cell growth substrate. In a preferred embodiment, the method
35 further includes contacting the cells with other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate
40 25 proteoglycan, glycosaminoglycans, epidermal growth factor or nerve growth factors, and peptide fragments thereof.

The cells may comprise primary cells or cell culture cell lines. The methods of this aspect of the invention can be used in vivo, ex vivo, or in vitro.
45

30 In a preferred embodiment, r-laminin 2 is used to coat the surface of a substrate, to promote cell adhesion to the substrate, and to stimulate cell proliferation/differentiation/stasis. The substrate used herein may be any desired substrate. For laboratory use, the substrate may be as simple as glass or plastic. For use in
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5 vivo, the substrate may be any biologically compatible material capable of supporting cell growth. Suitable substrate materials include shaped articles made of or coated with such materials as collagen, regenerated collagen, polyglycolic acid, polygalactose, polylactic acid or derivatives thereof; biocompatible metals such as titanium and stainless steel; 10 ceramic materials including prosthetic material such as hydroxylapatite; synthetic polymers including polyesters and nylons; polystyrene; polyacrylates; polytetrafluoroethylene and virtually any other material to which biological molecules can readily adhere.

15 In a further aspect, the present invention provides cell growth substrates for the adhesion and proliferation of cells in culture, by providing an amount effective of substantially purified laminin 2 for the attachment of cells to a cell culture device for the attachment and subsequent proliferation, differentiation, or stasis of the cells. The 20 substrates may comprise any of the substrates discussed above. Preferably, r-laminin 2 is coated on the surface of the substrate at a concentration of between about 1 ng/ml and about 10 µg/ml, and more preferably 1 ng/ml and about 10 µg/ml.

25 In another aspect of the present invention, an improved cell culture medium is provided, wherein the improvement comprises addition to the cell culture medium of an effective amount of substantially purified laminin 2 to the cell culture medium to promote the adherence, proliferation, differentiation, or stasis of cells. Any cell culture media that 30 can support the growth of cells can be used with the present invention. Such cell culture media include, but are not limited to Basal Media Eagle, Dulbecco's Modified Eagle Medium, Iscove's Modified Dulbecco's Medium, McCoy's Medium, Minimum Essential Medium, F-10 Nutrient Mixtures, Opti-MEM® Reduced-Serum Medium, RPMI Medium, 35 and Macrophage-SFM Medium or combinations thereof.

40 The improved cell culture medium can be supplied in either a concentrated (ie: 10X) or non-concentrated form, and may be supplied as either a liquid, a powder, or a lyophilizate. The cell culture may be either chemically defined, or may contain a serum supplement. Culture media is commercially available from many sources, such as GIBCO BRL (Gaithersburg, MD) and Sigma (St. Louis, MO). In an alternative embodiment, the 45 r-laminin 2 is used as a cell culture supplement.

50 The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

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Examples

Recombinant Laminin-2

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5 cDNAs coding for the complete open reading frame of the human $\beta 1$ chain and the human $\gamma 1$ chain have been described. (Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); Pikkarainen et al., J. Biol. Chem. 263:6751-6758 (1988); Pikkarainen et al., Eur. J. Biochem. 209:571-582 (1992)). The $\gamma 1$ cDNA was modified to contain a 3' end (corresponding to the C-terminal end) insertion coding for the FLAG peptide epitope tag (SEQ ID NO:25). The complete human laminin $\alpha 2$ cDNA was constructed from the large (approximately 2/3 of open reading frame) cDNA as described in (Vuolteenaho et al., J. Cell Biol. 124:381-394 (1994)) with the C-terminal (3'-end) cDNA as described in (Ehrig et al., Proc. Natl. Acad. Sci. 87:3264-3268 (1990)). The $\beta 1$, $\gamma 1$, and $\alpha 2$ cDNAs were inserted into the pCIS (Genentech, South San Francisco, CA), pRC-CMV, and pCEP4 (InVitrogen, Inc., Carlsbad, CA) mammalian expression vectors respectively. pRC-CMV contained a neo (G418) expression cassette and pCEP4 contained a puromycin expression cassette, each under a separate promoter. Transfection of human embryonic kidney 293 cells (adenovirus transformed, ATCC CRL 1573) with the $\gamma 1$ -FLAG expression vector was carried out by calcium phosphate precipitation in 35 mm plastic dishes as previously described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). Laminin $\gamma 1$ expressing stable clones were selected in the presence of G418 antibiotic. These cells were found to express the laminin $\gamma 1$ chain that reacted with both laminin and FLAG-specific antibodies in immunoblots. One such clone was subsequently co-transfected with the expression vector DNA coding for the $\alpha 2$ and $\beta 1$ laminin chains. New clones were selected in the presence of G418+ puromycin. A clone (designated #44) was determined to express all three laminin 2 chains, by using polyclonal antibodies specific for placental laminin and the $\alpha 2$ -G domain, $\beta 1$ chain, and FLAG epitope tag (Cheng et al., J. Biol. Chem. 272:31525-32 (1997); Rambukkana et al., Cell 88:811-821 (1997)). This clone was expanded in tissue culture. Conditioned serum-containing medium was collected and pooled for purification of secreted protein.

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Purification of recombinant laminin 2

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5 The procedure is described for 100 ml of pooled conditioned medium. Purification
was carried out at 4°-10°C in a cold room. A small column was packed with two ml of
heparin-Sepharose-4B beads and equilibrated with Tris-buffer (50 mM Tris-HCl, pH 7.4,
10 containing 1 mM EDTA and 0.1 mM PMSF) diluted 2:1 with water. The medium was
5 passed through the column. The column was then washed with several volumes of Tris-
buffer to decrease the NaCl concentration. One ml of anti-FLAG M2 agarose affinity gel
suspension (Sigma-Aldrich, St. Louis, MO) was added to the preparation and used to
15 absorb the recombinant protein bearing the FLAG epitope tag. After washing five times
with Tris-buffer, 0.1 mg (in one ml) of FLAG peptides (Sigma-Aldrich) was added to
20 elute the recombinant laminin protein from the beads. The protein was freed of peptides
with a spin column. Recombinant protein was characterized by SDS-polyacrylamide gel
electrophoresis (SDS-PAGE) (Figure 1), immunoblotting, and Pt/C rotary shadow
electron microscopy (Figure 2).

Recovered yields of recombinant laminin 2 were 6 µg/ml purified protein from
25 conditioned medium (determined from a 100 ml batch preparation). The recombinant
laminin had three Coomassie blue-staining bands, the larger corresponding to the α2
subunit. (Figure 1) Some unprocessed (i.e.: uncleaved) α2 chain was typically observed.
The cleaved version contained a high molecular weight band (approximately 300 kDa) and
30 a 75 kDa band, the latter the predicted G fragment. (Cheng et al., J. Biol. Chem.
272:31525-32 (1997) The two forms of laminin 2 could be separated from each other by
20 heparin affinity chromatography.

Figure 2 is an electron micrograph of purified r-laminin 2, which was dialyzed
35 into 0.15M ammonium bicarbonate, mixed with glycerol to a final ratio of 6:4
glycerol:buffer, and nebulized onto freshly cleaved mica. The sample was evacuated in a
25 Balzers BAF-500K freeze-etch unit and rotary shadowed at an 8° angle with 0.9 nm Pt/C
40 as described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). As can be
seen from the figure, r-laminin 2 demonstrates the cruciform structure that is typical of
endogenously expressed laminin molecules.

45 30 *Functional Data*

Recombinant laminin 2 was found to possess self-assembly activity in a co-
polymerization assay (Figure 3). A fixed trace amount of r-laminin 2 was mixed with
50 increasing concentrations of laminin 1 in separate tubes (each containing a small amount

5 of bovine serum albumin (BSA)) and incubated at 37°C as described (Cheng et al., J. Biol. Chem. 272:31525-32 (1997)). The incubation mixtures were then centrifuged in supernatant (S) and polymer pellet (P) fractions. Laminin 2 was detected with FLAG-specific antibody. At higher concentrations, increasing fractions of laminin 2 are detected
10 5 in the pellet fraction, evidence for laminin-type polymerization.

R-laminin 2 was also found to support adhesion and spreading of C2C12 myoblasts (Figure 4), but not HT1080 fibrosarcoma cells (data not shown). Cultured myoblasts were added to 96-well culture dishes previously coated with two preparations of
15 r-laminin 2 (two left bars), or with r-laminin 2 bearing different deletions of the G domain, all at 5 µg/ml. Deletion of G1-3 sub-domains (which bears the α7β1 integrin binding site), or all of G (which also removes the dystroglycan sites) greatly reduced binding.
20

Human laminin α2 polynucleotide and polypeptide

We have determined that the published sequence of the human laminin α2 nucleic
25 15 acid and protein sequences (Ehrig et al., PNAS 87:3264-3268 (1990)) are incorrect. An erroneous dropped G base that should lie near the 3' end of the nucleic acid sequence (Figure 5), leads to a prediction of a prematurely truncated laminin alpha2-G domain. The correct amino acid sequence for the α2 chain protein is shown in Figure 5.

One of the most serious consequences of the erroneous sequence may be that the
20 20 end of the G domain is predicted to lack a cysteine residue that is conserved in different laminins, and is present in the corrected sequence presented here. It is thought that this cysteine pairs with another cysteine in the G domain and is important for protein conformation. Furthermore, if the incorrect sequence is used, an epitope tag placed at the
35 apparent C-terminus will in fact be out of frame, and thus the epitope tag will not be
25 functional.

The present invention is not limited by the aforementioned particular preferred
45 30 embodiments. It will occur to those ordinarily skilled in the art that various modifications may be made to the disclosed preferred embodiments without diverting from the concept of the invention. All such modifications are intended to be within the scope of the present invention.

Claims

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We claim

1. Substantially purified laminin 2.
2. The substantially purified laminin 2 of claim 1, comprising recombinant laminin 2.
3. The substantially purified recombinant laminin 2 of claim 2 comprising:
a first chain comprising a polypeptide that is substantially similar to an $\alpha 2$ laminin chain;
a second chain comprising a polypeptide that is substantially similar to a $\beta 1$ laminin chain; and
a third chain comprising a polypeptide that is substantially similar to a $\gamma 1$ laminin chain;
wherein the first, second, and third chains are assembled into recombinant heterotrimeric laminin 2.
4. The substantially purified recombinant laminin 2 of claim 2 comprising:
a first chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, 11, or fragments thereof;
a second chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:13, 15, 17, 19 or fragments thereof; and
a third chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31 or fragments thereof;
wherein the first, second, and third chains are assembled into recombinant heterotrimeric laminin 2.
5. The substantially purified recombinant laminin 2 of claim 2 comprising:
a first chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:2, 4, 6, 8, 10, 12 or fragments thereof;
a second chain comprising a polypeptide at least 70% identical to one or more of

5 SEQ ID NO:14, 16, 18, 20 or fragments thereof; and
a third chain comprising a polypeptide at least 70% identical to one or more of
SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof;
wherein the first, second, and third chains are assembled into recombinant
10 5 heterotrimeric laminin 2.

15 6. The substantially purified recombinant laminin 2 of claim 2 comprising a first,
second, and third polypeptide chain, wherein the first, second, and third polypeptide
chains each comprise a general structure selected from the group consisting of: (1) R1-R2-
10 R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-
R3(e)

20 wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable
of directing secretion of the polypeptide, wherein the signal sequence may be the natural
signal sequence for the particular laminin chain, that of another secreted protein, or it may
15 25 be an artificial sequence; R3 is a secreted $\alpha 2$ laminin chain for the first polypeptide chain,
a secreted $\beta 1$ laminin chain for the second polypeptide chain, and $\gamma 1$ laminin chain for the
third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag.

30 7. Recombinant laminin 2-expressing host cells.

20 8. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells
express recombinant laminin 2 comprising:

35 a first chain comprising a recombinant polypeptide that is substantially similar an
laminin $\alpha 2$ polypeptide;

25 a second chain comprising a recombinant polypeptide that is substantially similar
40 to a laminin $\beta 1$ polypeptide sequence; and

a third chain comprising a recombinant polypeptide that is substantially similar to a
laminin $\gamma 1$ polypeptide sequence;

45 wherein the cell expresses the first, second, and third chains, and wherein the first,
30 second, and third chains assemble into recombinant laminin 2 that is secreted into the
media by the cultured cell.

5 9. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising:

10 a first chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, 11, or fragments thereof;

15 a second chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 15, 17, 19, or fragments thereof; and

20 a third chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, or fragments thereof;

25 wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell.

15 10. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising:

30 a first chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:2, 4, 6, 8, 10, 12, or fragments thereof;

20 a second chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:14, 16, 18, 20, or fragments thereof; and

35 a third chain comprising a recombinant polypeptide at least 70% identical to one or more of SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof;

40 wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell.

45 11. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

5 wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable
of directing secretion of the polypeptide, wherein the signal sequence may be the natural
signal sequence for the particular laminin chain, that of another secreted protein, or it may
be an artificial sequence; R3 is a secreted $\alpha 2$ laminin chain for the first polypeptide chain,
10 5 a secreted $\beta 1$ laminin chain for the second polypeptide chain, and $\gamma 1$ laminin chain for the
third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag .

15 12. The host cells of any of claims 7-11, wherein the host cell is a mammalian cell.

20 13. The host cells of claim 12, wherein at least one of the first, second, or third chains
is expressed as a fusion protein with an epitope tag.

25 14. A method of purifying recombinant laminin 2, comprising:

a. providing the host cells of claim 12;

15 b. growing the cells in cell culture medium under conditions to stimulate
expression of the recombinant laminin 2 chains;

30 c. passing the cell culture medium through an affinity chromatography
20 column, wherein the column contains a compound that binds to the recombinant laminin
2;

35 d. washing the affinity column to remove unbound materials; and

25 e. eluting the bound recombinant laminin 2 from the column.

40 15. Substantially purified recombinant laminin 2 isolated according to the method of
claim 14.

45 30 16. A pharmaceutical composition comprising:

a. laminin 2; and

b. a pharmaceutically acceptable carrier.

- 5 17. The pharmaceutical composition of claim 16, wherein the laminin 2 comprises recombinant laminin 2.
- 10 18. A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote nerve regeneration.
- 15 19. A method for regulating angiogenesis, comprising contacting a tissue in need thereof with an amount effective to regulate angiogenesis of the laminin 2 of any of claims 1-5 and 15 to regulate angiogenesis.
- 20 20. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device.
- 25 21. An improved medical device, comprising a medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device.
- 30 22. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell adhesion to a surface.
- 35 23. An improved cell growth surface, wherein the improvement consists of providing a cell growth surface that has been coated with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell attachment to the cell growth surface.
- 40 24. A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the pharmaceutical composition of claim 16 or 17 to promote nerve regeneration.
- 45 30

- 5 25. A method for regulating angiogenesis, comprising contacting a tissue in need thereof with an amount effective to regulate angiogenesis of the pharmaceutical composition of claim 16 or 17 to regulate angiogenesis.
- 10 26. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device.
- 15 27. An improved medical device, comprising a medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device.
- 20 28. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell adhesion to a surface.
- 25 29. An improved cell growth surface, wherein the improvement consists of providing a cell growth surface that has been coated with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell attachment to the cell growth surface.
- 30 30. An isolated recombinant laminin $\alpha 2$ chain polynucleotide consisting essentially of the sequence shown in SEQ ID NO:1.
- 35 31. A substantially purified laminin $\alpha 2$ chain polypeptide consisting essentially of the sequence shown in SEQ ID NO:2.
- 25 32. An expression vector comprising the polynucleotide of SEQ ID NO:1.
- 40 33. A host cell transfected with the expression vector of claim 32.
- 45 34. A method for treating degenerative muscle disorders in a mammal, comprising administering the host cells of any of claims 7-13 and 33 to a mammal in need thereof, wherein the host cells secrete an amount effective of the recombinant laminin 2 or the recombinant laminin $\alpha 2$ chain polypeptide, to treat the degenerative muscle disorder.

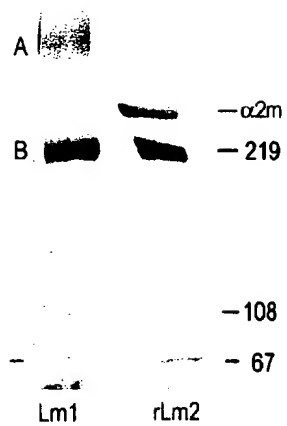


FIG. 1



FIG. 2

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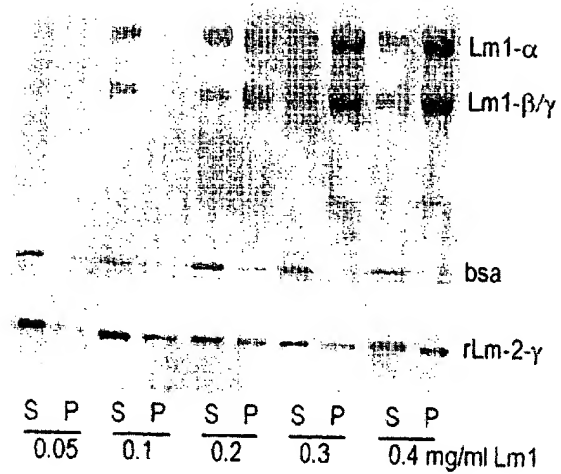


FIG.3

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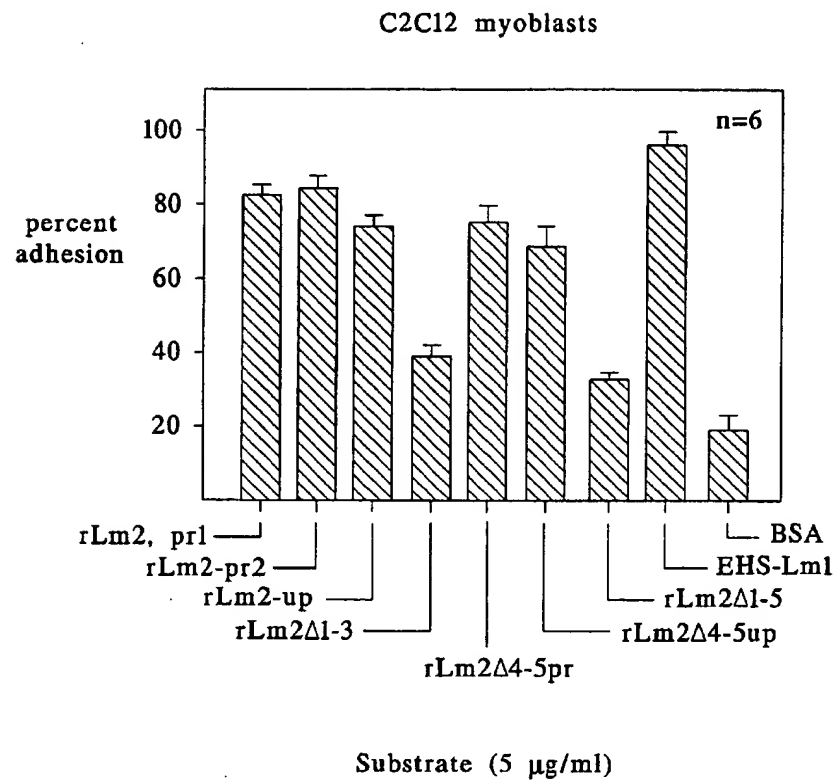
FIG. 4

FIG.5

5'		12		21	31	41	51
+3	R S L	K L T	K G T	A S H W	R L I	L P R	
1	TCAGATCCCT	GAAGCTCACC	AAAGGCACAG	CAAGCCCACTG	GAGGTTAATT	TTGCCCAAGGC	
	AGTCTAGGGA	CTTCGAGTGG	TTTCCCGTGTC	GTTCGGTGAC	CTCCAATTAA	AACGGTTCCG	
5'		71	81	91	1	11	
+3	P W N &						
61	CCTGGAAC TG	A					
	GGACCTTGAC	T					

Site of
missing
base-pair

SEQUENCE LISTING

<110> Yurchenco, Peter

<120> Laminin 2 and Methods For Its Use

<130> 99,274-B1

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<160> 32

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 Ala Ala Gly Val Leu Leu Leu Leu Leu Ser Gly Gly Leu Gly Gly
 5 10 15

gta cag gcg cag cgg ccg cag cag cag cgg cag tca cag gca cat cag 154
 Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln Ala His Gln
 20 25 30 35

caa aga ggt tta ttc cct gct gtc ctg aat ctt gct tct aat gct ctt 202
 Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu
 40 45 50

atc acg acc aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc 250
 Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys
 55 60 65

aaa ttg gta gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt 298
 Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys
 70 75 80

cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att 346
 Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile
 85 90 95

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 Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile
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aag aat gga atc gaa tac cat tat gtg aca att aca ctg gat tta cag	442
Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln	
120 125 130	
cag gtg ttc cag atc gcg tat gtg att gtg aag gca gct aac tcc ccc	490
Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro	
135 140 145	
cgg cct gga aac tgg att ttg gaa cgc tct ctt gat gat gtt gaa tac	538
Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr	
150 155 160	
aag ccc tgg cag tat cat gct gtg aca gac acg gag tgc cta acg ctt	586
Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu	
165 170 175	
tac aat att tat ccc cgc act ggg cca ccg tca tat gcc aaa gat gat	634
Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp	
180 185 190 195	
gag gtc atc tgc act tca ttt tac tcc aag ata cac ccc tta gaa aat	682
Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn	
200 205 210	
gga gag att cac atc tct tta atc aat ggg aga cca agt gcc gat gat	730
Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp	
215 220 225	
cct tct cca gaa ctg cta gaa ttt acc tcc gct cgc tat att cgc ctg	778
Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu	
230 235 240	
aga ttt cag agg atc cgc aca ctg aat gct gac ttg atg atg ttt gct	826
Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala	
245 250 255	
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His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr	
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Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly	
280 285 290	
cat gcc agg gct tgt cca ctt gat cca gcg aca aat aaa tct cgc tgt	970
His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys	
295 300 305	
gag tgt gag cat aac aca tgt ggc gat agc tgt gat cag tgc tgt cca	1018
Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro	
310 315 320	
gga ttc cat cag aaa ccc tgg aga gct gga act ttt cta act aaa act	1066
Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr	
325 330 335	
gaa tgt gaa gca tgc aat tgt cat gga aaa gct gaa gaa tgc tat tat	1114
Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr	
340 345 350 355	
gat gaa aat gtt gcc aga aga aat ctg agt ttg aat ata cgt gga aag	1162

Asp	Glu	Asn	Val	Ala	Arg	Arg	Asn	Leu	Ser	Leu	Asn	Ile	Arg	Gly	Lys	
				360					365					370		
tac	att	gga	ggg	ggg	gtc	tgc	att	aat	tgt	acc	caa	aac	act	gct	ggg	1210
Tyr	Ile	Gly	Gly	Gly	Val	Cys	Ile	Asn	Cys	Thr	Gln	Asn	Thr	Ala	Gly	
			375					380					385			
ata	aac	tgc	gag	aca	tgt	aca	gat	ggc	ttc	ttc	aga	ccc	aaa	ggg	gta	1258
Ile	Asn	Cys	Glu	Thr	Cys	Thr	Asp	Gly	Phe	Phe	Arg	Pro	Lys	Gly	Val	
			390				395					400				
tct	cca	aat	tat	cca	agg	cca	tgc	cag	cca	tgt	cat	tgc	gat	cca	att	1306
Ser	Pro	Asn	Tyr	Pro	Arg	Pro	Cys	Gln	Pro	Cys	His	Cys	Asp	Pro	Ile	
	405				410						415					
ggg	tcc	tta	aat	gaa	gtc	tgt	gtc	aag	gat	gag	aaa	cat	gct	cga	cga	1354
Gly	Ser	Leu	Asn	Glu	Val	Cys	Val	Lys	Asp	Glu	Lys	His	Ala	Arg	Arg	
	420				425				430					435		
ggg	ttg	gca	cct	gga	tcc	tgt	cat	tgc	aaa	act	ggg	ttt	gga	ggg	gtg	1402
Gly	Leu	Ala	Pro	Gly	Ser	Cys	His	Cys	Lys	Thr	Gly	Phe	Gly	Gly	Val	
			440					445					450			
agc	tgt	gat	cgg	tgt	gcc	agg	ggc	tac	act	ggc	tac	ccg	gac	tgc	aaa	1450
Ser	Cys	Asp	Arg	Cys	Ala	Arg	Gly	Tyr	Thr	Gly	Tyr	Pro	Asp	Cys	Lys	
			455				460					465				
gcc	tgt	aac	tgc	agt	ggg	tta	ggg	agc	aaa	aat	gag	gat	cct	tgt	ttt	1498
Ala	Cys	Asn	Cys	Ser	Gly	Leu	Gly	Ser	Lys	Asn	Glu	Asp	Pro	Cys	Phe	
		470				475					480					
ggc	ccc	tgt	atc	tgc	aag	gaa	aat	gtt	gaa	gga	gga	gac	tgt	agt	cgt	1546
Gly	Pro	Cys	Ile	Cys	Lys	Glu	Asn	Val	Glu	Gly	Gly	Asp	Cys	Ser	Arg	
	485				490				495							
tgc	aaa	tcc	ggc	ttc	ttc	aat	ttg	caa	gag	gat	aat	tgg	aaa	ggc	tgc	1594
Cys	Lys	Ser	Gly	Phe	Phe	Asn	Leu	Gln	Glu	Asp	Asn	Trp	Lys	Gly	Cys	
	500				505				510					515		
gat	gag	tgt	ttc	tgt	tca	ggg	gtt	tca	aac	aga	tgt	cag	agt	tcc	tac	1642
Asp	Glu	Cys	Phe	Cys	Ser	Gly	Val	Ser	Asn	Arg	Cys	Gln	Ser	Ser	Tyr	
			520					525					530			
tgg	acc	tat	ggc	aaa	ata	caa	gat	atg	agt	ggc	tgg	tat	ctg	act	gac	1690
Trp	Thr	Tyr	Gly	Lys	Ile	Gln	Asp	Met	Ser	Gly	Trp	Tyr	Leu	Thr	Asp	
			535				540						545			
ctt	cct	ggc	cgc	att	cga	gtg	gct	ccc	cag	cag	gac	gac	ttg	gac	tca	1738
Leu	Pro	Gly	Arg	Ile	Arg	Val	Ala	Pro	Gln	Gln	Asp	Asp	Leu	Asp	Ser	
		550				555					560					
cct	cag	cag	atc	agc	atc	agt	aac	gcg	gag	gcc	cgg	caa	gcc	ctg	cgg	1786
Pro	Gln	Gln	Ile	Ser	Ile	Ser	Asn	Ala	Glu	Ala	Arg	Gln	Ala	Leu	Pro	
		565				570				575						
cac	agc	tac	tac	tgg	agc	gcg	ccg	gct	ccc	tat	ctg	gga	aac	aaa	ctc	1834
His	Ser	Tyr	Tyr	Trp	Ser	Ala	Pro	Ala	Pro	Tyr	Leu	Gly	Asn	Lys	Leu	
	580				585				590					595		
cca	gca	gta	gga	gga	cag	ttg	aca	ttt	acc	ata	tca	tat	gac	ctt	gaa	1882
Pro	Ala	Val	Gly	Gly	Gln	Leu	Thr	Phe	Thr	Ile	Ser	Tyr	Asp	Leu	Glu	

600	605	610	
gaa gag gaa gaa gat aca gaa cgt gtt ctc cag ctt atg att atc tta Glu Glu Glu Glu Asp Thr Glu Arg Val Leu Gln Leu Met Ile Ile Leu 615 620 625			1930
gag ggt aat gac ttg agc atc agc aca gcc caa gat gag gtg tac ctg Glu Gly Asn Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu Val Tyr Leu 630 635 640			1978
cac cca tct gaa gaa cat act aat gta ttg tta ctt aaa gaa gaa tca His Pro Ser Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser 645 650 655			2026
ttt acc ata cat ggc aca cat ttt cca gtc cgt aga aag gaa ttt atg Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met 660 665 670 675			2074
aca gtg ctt gcg aat ttg aag aga gtc ctc cta caa atc aca tac agc Thr Val Leu Ala Asn Leu Lys Arg Val Leu Leu Gln Ile Thr Tyr Ser 680 685 690			2122
ttt ggg atg gat gcc atc ttc agg ttg agc tct gtt aac ctt gaa tcc Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser 695 700 705			2170
gct gtc tcc tat cct act gat gga agc att gca gca gct gta gaa gtg Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Val Glu Val 710 715 720			2218
tgt cag tgc cca cca ggg tat act ggc tcc tct tgt gaa tct tgt tgg Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp 725 730 735			2266
cct agg cac agg cga gtt aac ggc act att ttt ggt ggc atc tgt gag Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu 740 745 750 755			2314
cca tgt cag tgc ttt ggt cat gcg gag tcc tgt gat gac gtc act gga Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp Val Thr Gly 760 765 770			2362
gaa tgc ctg aac tgt aag gat cac aca ggt ggc cca tat tgt gat aaa Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys 775 780 785			2410
tgt ctt cct ggt ttc tat ggc gag cct act aaa gga acc tct gaa gac Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp 790 795 800			2458
tgt caa ccc tgt gcc tgt cca ctc aat atc cca tcc aat aac ttt agc Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser 805 810 815			2506
cca acg tgc cat tta gac cgg agt ctt gga ttg atc tgt gat gga tgc Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys 820 825 830 835			2554
cct gtc ggg tac aca gga cca cgc tgt gag agg tgt gca gaa ggc tat Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr 840 845 850			2602

ttt gga caa ccc tct gta cct gga gga tca tgt cag cca tgc caa tgc	2650
Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys	
855 860 865	
aat gac aac ctt gac ttc tcc atc cct ggc agc tgt gac agc ttg tct	2698
Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser	
870 875 880	
ggc tcc tgt ctg ata tgt aaa cca ggt aca aca ggc cgg tac tgt gag	2746
Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu	
885 890 895	
ctc tgt gct gat gga tat ttt gga gat gca gtt gat gcg aag aac tgt	2794
Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys	
900 905 910 915	
cag ccc tgt cgc tgt aat gcc ggt ggc tct ttc tct gag gtt tgc cac	2842
Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His	
920 925 930	
agt caa act gga cag tgt gag tgc aga gcc aac gtt cag ggt cag aga	2890
Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg	
935 940 945	
tgt gac aaa tgc aag gct ggg acc ttt ggc cta caa tca gca agg ggc	2938
Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly	
950 955 960	
tgt gtt ccc tgc aac tgc aat tct ttt ggg tct aag tca ttc gac tgt	2986
Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys	
965 970 975	
gaa gag agt gga caa tgt tgg tgc caa cct gga gtc aca ggg aag aaa	3034
Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys	
980 985 990 995	
tgt gac cgc tgt gcc cac ggc tat ttc aac ttc caa gaa gga ggc tgc	3082
Cys Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys	
1000 1005 1010	
aca gct tgt gaa tgt tct cat ctg ggt aat aat tgt gac cca aag act	3130
Thr Ala Cys Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr	
1015 1020 1025	
ggg cga tgc att tgc cca ccc aat acc att gga gag aaa tgt tct aaa	3178
Gly Arg Cys Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys	
1030 1035 1040	
tgt gca ccc aat acc tgg ggc cac agc att acc act ggt tgt aag gct	3226
Cys Ala Pro Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala	
1045 1050 1055	
tgt aac tgc agc aca gtg gga tcc ttg gat ttc caa tgc aat gta aat	3274
Cys Asn Cys Ser Thr Val Gly Ser Leu Asp Phe Gln Cys Asn Val Asn	
1060 1065 1070 1075	
aca ggc caa tgc aac tgt cat cca aaa ttc tct ggt gca aaa tgt aca	3322
Thr Gly Gln Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr	
1080 1085 1090	

gag tgc agt cga ggt cac tgg aac tac cct cgc tgc aat ctc tgt gac 3370
 Glu Cys Ser Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp
 1095 1100 1105

tgc ttc ctc cct ggg aca gat gcc aca acc tgt gat tca gag act aaa 3418
 Cys Phe Leu Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser Glu Thr Lys
 1110 1115 1120

aaa tgc tcc tgt agt gat caa act ggg cag tgc act tgt aag gtg aat 3466
 Lys Cys Ser Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys Lys Val Asn
 1125 1130 1135

gtg gaa ggc atc cac tgt gac aga tgc cgg cct ggc aaa ttc gga ctc 3514
 Val Glu Gly Ile His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu
 1140 1145 1150 1155

gat gcc aag aat cca ctt ggc tgc agc agc tgc tat tgc ttc ggc act 3562
 Asp Ala Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr
 1160 1165 1170

act acc cag tgc tct gaa gca aaa gga ctg atc cgg acg tgg gtg act 3610
 Thr Thr Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr
 1175 1180 1185

ctg aag gct gag cag acc att cta ccc ctg gta gat gag gct ctg cag 3658
 Leu Lys Ala Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln
 1190 1195 1200

cac acg acc acc aag ggc att gtt ttt caa cat cca gag att gtt gcc 3706
 His Thr Thr Thr Lys Gly Ile Val Phe Gln His Pro Glu Ile Val Ala
 1205 1210 1215

cac atg gac ctg atg aga gaa gat ctc cat ttg gaa cct ttt tat tgg 3754
 His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp
 1220 1225 1230 1235

aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc 3802
 Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly
 1240 1245 1250

aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc 3850
 Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe
 1255 1260 1265

tct aca tat aat cct caa gtg atc att cga ggt ggg aca cct act cat 3898
 Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His
 1270 1275 1280

gct aga att atc gtc agg cat atg gct gct cct ctg att ggc caa ttg 3946
 Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu
 1285 1290 1295

aca agg cat gaa att gaa atg aca gag aaa gaa tgg aaa tat tat ggg 3994
 Thr Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly
 1300 1305 1310 1315

gat gat cct cga gtc cat aga act gtg acc cga gaa gac ttc ttg gat 4042
 Asp Asp Pro Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp
 1320 1325 1330

ata cta tat gat att cat tac att ctt atc aaa gct act tat gga aat 4090

Ile Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn	
1335 1340 1345	
ttc atg cga caa agc agg att tct gaa atc tca atg gag gta gct gaa	4138
Phe Met Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu	
1350 1355 1360	
caa gga cgt gga aca aca atg act cct cca gct gac ttg att gaa aaa	4186
Gln Gly Arg Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys	
1365 1370 1375	
tgt gat tgt ccc ctg ggc tat tct ggc ctg tcc tgt gag gca tgc ttg	4234
Cys Asp Cys Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu	
1380 1385 1390 1395	
ccg gga ttt tat cga ctg cgt tct caa cca ggt ggc cgc acc cct gga	4282
Pro Gly Phe Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly	
1400 1405 1410	
cca acc ctg ggc acc tgt gtt cca tgt caa tgt aat gga cac agc agc	4330
Pro Thr Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser	
1415 1420 1425	
ctg tgt gac cct gaa aca tcg ata tgc cag aat tgt caa cat cac act	4378
Leu Cys Asp Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr	
1430 1435 1440	
gct ggt gac ttc tgt gaa cga tgt gct ctt gga tac tat gga att gtc	4426
Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val	
1445 1450 1455	
aag gga ttg cca aat gac tgt cag caa tgt gcc tgc cct ctg att tct	4474
Lys Gly Leu Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser	
1460 1465 1470 1475	
tcc agt aac aat ttc agc ccc tct tgt gtc gca gaa gga ctt gac gac	4522
Ser Ser Asn Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp	
1480 1485 1490	
tac cgc tgc acg gct tgt cca cgg gga tat gaa ggc cag tac tgt gaa	4570
Tyr Arg Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu	
1495 1500 1505	
agg tgt gcc cct ggc tat act ggc agt cca ggc aac cct gga ggc tcc	4618
Arg Cys Ala Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser	
1510 1515 1520	
tgc caa gaa tgt gag tgt gat ccc tat ggc tca ctg cct gtg ccc tgt	4666
Cys Gln Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys	
1525 1530 1535	
gac cct gtc aca gga ttc tgc acg tgc cga cct gga gcc acg gga agg	4714
Asp Pro Val Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg	
1540 1545 1550 1555	
aag tgt gac ggc tgc aag cac tgg cat gca cgc gag ggc tgg gag tgt	4762
Lys Cys Asp Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys	
1560 1565 1570	
gtt ttt tgt gga gat gag tgc act ggc ctt ctt ctc ggt gac ttg gct	4810
Val Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala	

1575	1580	1585	
cgc ctg gag cag atg gtc atg agc atc aac ctc act ggt ccg ctg cct			4858
Arg Leu Glu Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro			
1590	1595	1600	
gcg cca tat aaa atg ctg tat ggt ctt gaa aat atg act cag gag cta			4906
Ala Pro Tyr Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu			
1605	1610	1615	
aag cac ttg ctg tca cct cag cgg gcc cca gag agg ctt att cag ctg			4954
Lys His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu			
1620	1625	1630	1635
gca gag ggc aat ctg aat aca ctc gtg acc gaa atg aac gag ctg ctg			5002
Ala Glu Gly Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu			
1640	1645	1650	
acc agg gct acc aaa gtg aca gca gat ggc gag cag acc gga cag gat			5050
Thr Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp			
1655	1660	1665	
gct gag agg acc aac aca aga gca aag tcc ctg gga gaa ttc att aag			5098
Ala Glu Arg Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys			
1670	1675	1680	
gag ctt gcc cgg gat gca gaa gct gta aat gaa aaa gct ata aaa cta			5146
Glu Leu Ala Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu			
1685	1690	1695	
aat gaa act cta gga act cga gac gag gcc ttt gag aga aat ttg gaa			5194
Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu			
1700	1705	1710	1715
ggg ctt cag aaa gag att gac cag atg att aaa gaa ctg agg agg aaa			5242
Gly Leu Gln Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys			
1720	1725	1730	
aat cta gag aca caa aag gaa att gct gaa gat gag ttg gta gct gca			5290
Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala			
1735	1740	1745	
gaa gcc ctt ctg aaa aaa gtg aag aag ctg ttt gga gag tcc cgg ggg			5338
Glu Ala Leu Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly			
1750	1755	1760	
gaa aat gaa gaa atg gag aag gat ctc cgg gaa aaa ctg gct gac tac			5386
Glu Asn Glu Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr			
1765	1770	1775	
aaa aac aaa gtt gat gat gct tgg gac ctt ttg aga gaa gcc aca gat			5434
Lys Asn Lys Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp			
1780	1785	1790	1795
aaa atc aga gaa gct aat cgc cta ttt gca gta aat cag aaa aac atg			5482
Lys Ile Arg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met			
1800	1805	1810	
act gca ttg gag aaa aag aag gag gct gtt gag agc ggc aaa cga caa			5530
Thr Ala Leu Glu Lys Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln			
1815	1820	1825	

att gag aac act tta aaa gaa ggc aat gac ata ctc gat gaa gcc aac Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn 1830 1835 1840	5578
cgt ctt gca gat gaa atc aac tcc atc ata gac tat gtt gaa gac atc Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile 1845 1850 1855	5626
caa act aaa ttg cca cct atg tct gag gag ctt aat gat aaa ata gat Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp 1860 1865 1870 1875	5674
gac ctc tcc caa gaa ata aag gac agg aag ctt gct gag aag gtg tcc Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser 1880 1885 1890	5722
cag gct gag agc cac gca gct cag ttg aat gac tca tct gct gtc ctt Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ala Val Leu 1895 1900 1905	5770
gat gga atc ctt gat gag gct aaa aac atc tcc ttc aat gcc act gca Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala 1910 1915 1920	5818
gcc ttc aaa gct tac agc aat att aag gac tat att gat gaa gct gag Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu 1925 1930 1935	5866
aaa gtt gcc aaa gaa gcc aaa gat ctt gca cat gaa gct aca aaa ctg Lys Val Ala Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu 1940 1945 1950 1955	5914
gca aca ggt cct cgg ggt tta tta aag gaa gat gcc aaa ggc tgt ctt Ala Thr Gly Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu 1960 1965 1970	5962
cag aaa agc ttc agg att ctt aac gaa gcc aag aag tta gca aat gat Gln Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp 1975 1980 1985	6010
gta aaa gaa aat gaa gac cat cta aat ggc tta aaa acc agg ata gaa Val Lys Glu Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu 1990 1995 2000	6058
aat gct gat gct aga aat ggg gat ctc ttg aga act ttg aat gac act Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr 2005 2010 2015	6106
ttg gga aag tta tca gct att cca aat gat aca gct gct aaa ctg caa Leu Gly Lys Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln 2020 2025 2030 2035	6154
gct gtt aag gac aaa gcc aga caa gcc aac gac aca gct aaa gat gta Ala Val Lys Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val 2040 2045 2050	6202
ctg gca cag att aca gag ctc cac cag aac ctc gat ggc ctg aag aag Leu Ala Gln Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys 2055 2060 2065	6250

aat tac aat aaa cta gca gac agc gtc gcc aaa acg aat gct gtg gtt Asn Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val 2070 2075 2080	6298
aaa gat cct tcc aag aac aaa atc att gcc gat gca gat gcc act gtc Lys Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val 2085 2090 2095	6346
aaa aat tta gaa cag gaa gct gac cgg cta ata gat aaa ctc aaa ccc Lys Asn Leu Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro 2100 2105 2110 2115	6394
atc aag gaa ctt gag gat aac cta aag aaa aac atc tct gag ata aag Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys 2120 2125 2130	6442
gaa ttg ata aac caa gct cgg aaa caa gcc aat tct atc aaa gta tct Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser 2135 2140 2145	6490
gtg tct tca gga ggt gac tgc att cga aca tac aaa cca gaa atc aag Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys 2150 2155 2160	6538
aaa gga agt tac aat aat att gtt gtc aac gta aag aca gct gtt gct Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala 2165 2170 2175	6586
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Thr Glu Ile Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile	

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Pro Ala Glu Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe			
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Ser His Ile Ala Ile Ala Phe Asp Asp Thr Lys Val Lys Asn Arg Leu			
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Thr Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe			
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Ala Leu Glu
3110

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Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu
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Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn
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Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg
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His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser
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Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu
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Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala
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Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp
145 150 155 160

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 Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala
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 Lys Asp Asp Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro
 195 200 205
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 Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr
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 Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile
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 Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln
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 Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val
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 Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys
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 Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly
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 Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe
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 Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly
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Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile	
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Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp	
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Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys	
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Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser Phe Thr Ile	
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His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met Thr Val Leu	
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Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys			
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Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln			
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Pro Asn Asp Cys Gln Cys Ala Cys Pro Leu Ile Ser Ser Ser Asn	
1445 1450 1455	
aat ttc agc ccc tct tgt gtc gca gaa gga ctt gac gac tac cgc tgc	4416
Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp Tyr Arg Cys	
1460 1465 1470	
acg gct tgt cca cgg gga tat gaa ggc cag tac tgt gaa agg tgt gcc	4464
Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala	
1475 1480 1485	
cct ggc tat act ggc agt cca ggc aac cct gga ggc tcc tgc caa gaa	4512
Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser Cys Gln Glu	
1490 1495 1500	
tgt gag tgt gat ccc tat ggc tca ctg cct gtg ccc tgt gac cct gtc	4560
Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Pro Val	
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Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp	
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ggc tgc aag cac tgg cat gca cgc gag ggc tgg gag tgt gtt ttt tgt	4656
Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys Val Phe Cys	
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Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala Arg Leu Glu	
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Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr	
1570 1575 1580	
aaa atg ctg tat ggt ctt gaa aat atg act cag gag cta aag cac ttg	4800
Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu Lys His Leu	
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ctg tca cct cag cgg gcc cca gag agg ctt att cag ctg gca gag ggc	4848
Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly	
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aat ctg aat aca ctc gtg acc gaa atg aac gag ctg ctg acc agg gct	4896
Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu Thr Arg Ala	
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Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg	

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Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys Glu Leu Ala			
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Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu Asn Glu Thr			
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Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu Gly Leu Gln			
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Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys Asn Leu Glu			
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Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala Glu Ala Leu			
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Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly Glu Asn Glu			
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gaa atg gag aag gat ctc cgg gaa aaa ctg gct gac tac aaa aac aaa			5280
Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys			
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gtt gat gat gct tgg gac ctt ttg aga gaa gcc aca gat aaa atc aga			5328
Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Ile Arg			
1765	1770	1775	
gaa gct aat cgc cta ttt gca gta aat cag aaa aac atg act gca ttg			5376
Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu			
1780	1785	1790	
gag aaa aag aag gag gct gtt gag agc ggc aaa cga caa att gag aac			5424
Glu Lys Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn			
1795	1800	1805	
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Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala			
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gat gaa atc aac tcc atc ata gac tat gtt gaa gac atc caa act aaa			5520
Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys			
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Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser			
1845	1850	1855	
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Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu			
1860	1865	1870	
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Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile			
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 Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys
 1890 1895 1900

gct tac agc aat att aag gac tat att gat gaa gct gag aaa gtt gcc 5760
 Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala
 1905 1910 1915 1920

aaa gaa gcc aaa gat ctt gca cat gaa gct aca aaa ctg gca aca ggt 5808
 Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly
 1925 1930 1935

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 Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser
 1940 1945 1950

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 Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu
 1955 1960 1965

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 1970 1975 1980

gct aga aat ggg gat ctc ttg aga act ttg aat gac act ttg gga aag 6000
 Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys
 1985 1990 1995 2000

tta tca gct att cca aat gat aca gct gct aaa ctg caa gct gtt aag 6048
 Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys
 2005 2010 2015

gac aaa gcc aga caa gcc aac gac aca gct aaa gat gta ctg gca cag 6096
 Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln
 2020 2025 2030

att aca gag ctc cac cag aac ctc gat ggc ctg aag aag aat tac aat 6144
 Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn
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 Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro
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 2065 2070 2075 2080

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 2085 2090 2095

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 2100 2105 2110

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 2115 2120 2125

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gct ctt ctg atg tat ctt gcc aca cga gac ctg aga gat ttc atg agt Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp Phe Met Ser 2355 2360 2365	7104
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Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser	
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2385 2390 2395 2400	
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Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile	
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Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile Arg Pro Glu	
2580 2585 2590	
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Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val Glu Arg	
2595 2600 2605	
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Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg Arg Tyr Met	

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Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile Pro			
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Pro Phe Glu Gly Cys Ile Trp Asn Leu Val Ile Asn Ser Val Pro Met			
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Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile Gly Arg Cys			
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Ala Ile Ala Phe Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu			
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Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Ala			
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 Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val
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 Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys
 50 55 60
 Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile Thr Asn Ala
 65 70 75 80
 Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly
 85 90 95
 Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe
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 Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly
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 Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp
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 Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile
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 His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro
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 Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln
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 Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp
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 Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val
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 Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg
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Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu
 275 280 285
 His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His
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 Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu
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 Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly
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 Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly Asn Lys Leu Pro Ala Val
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 Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu
 580 585 590
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Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser Phe Thr Ile		
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His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met Thr Val Leu		
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Ala Asn Leu Lys Arg Val Leu Leu Gln Ile Thr Tyr Ser Phe Gly Met		
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Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Ala Val Ser		
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Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys		
690	695	700
Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp Pro Arg His		
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Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln		
725	730	735
Cys Phe Gly His Ala Glu Ser Cys Asp Asp Val Thr Gly Glu Cys Leu		
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Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys Cys Leu Pro		
755	760	765
Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp Cys Gln Pro		
770	775	780
Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys		
785	790	795
His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly		
805	810	815
Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln		
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Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn		
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Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys		
850	855	860
Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala		
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Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys		
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Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr		
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Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys		
915	920	925

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 Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr Thr Thr Gln
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Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu Thr Arg Ala		
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Pro Tyr Phe Ser Tyr Asp	Leu Gly Ser Gly Asp	Thr His Thr Met Ile	
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Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln Ala His Gln	
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Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu	
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Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys	
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Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys	
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Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile	
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Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile	
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Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe	
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				680				685					690				
ttt	ggg	atg	gat	gcc	atc	ttc	agg	ttg	agc	tct	gtt	aac	ctt	gaa	tcc	2170	
Phe	Gly	Met	Asp	Ala	Ile	Phe	Arg	Leu	Ser	Ser	Val	Asn	Leu	Glu	Ser		
			695					700					705				
gct	gtc	tcc	tat	cct	act	gat	gga	agc	att	gca	gca	gct	gta	gaa	gtg	2218	
Ala	Val	Ser	Tyr	Pro	Thr	Asp	Gly	Ser	Ile	Ala	Ala	Ala	Val	Glu	Val		
			710				715					720					
tgt	cag	tgc	cca	cca	ggg	tat	act	ggc	tcc	tct	tgt	gaa	tct	tgt	tgg	2266	
Cys	Gln	Cys	Pro	Pro	Gly	Tyr	Thr	Gly	Ser	Ser	Cys	Glu	Ser	Cys	Trp		

725	730	735	
cct agg cac agg cga gtt aac ggc act att ttt ggt ggc atc tgt gag Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu 740 745 750 755			2314
cca tgt cag tgc ttt ggt cat gcg gag tcc tgt gat gac gtc act gga Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp Val Thr Gly 760 765 770			2362
gaa tgc ctg aac tgt aag gat cac aca ggt ggc cca tat tgt gat aaa Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys 775 780 785			2410
tgt ctt cct ggt ttc tat ggc gag cct act aaa gga acc tct gaa gac Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp 790 795 800			2458
tgt caa ccc tgt gcc tgt cca ctc aat atc cca tcc aat aac ttt agc Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser 805 810 815			2506
cca acg tgc cat tta gac cgg agt ctt gga ttg atc tgt gat gga tgc Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys 820 825 830 835			2554
cct gtc ggg tac aca gga cca cgc tgt gag agg tgt gca gaa ggc tat Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr 840 845 850			2602
ttt gga caa ccc tct gta cct gga gga tca tgt cag cca tgc caa tgc Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys 855 860 865			2650
aat gac aac ctt gac ttc tcc atc cct ggc agc tgt gac agc ttg tct Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser 870 875 880			2698
ggc tcc tgt ctg ata tgt aaa cca ggt aca aca ggc cgg tac tgt gag Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu 885 890 895			2746
ctc tgt gct gat gga tat ttt gga gat gca gtt gat gcg aag aac tgt Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys 900 905 910 915			2794
cag ccc tgt cgc tgt aat gcc ggt ggc tct ttc tct gag gtt tgc cac Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His 920 925 930			2842
agt caa act gga cag tgt gag tgc aga gcc aac gtt cag ggt cag aga Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg 935 940 945			2890
tgt gac aaa tgc aag gct ggg acc ttt ggc cta caa tca gca agg ggc Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly 950 955 960			2938
tgt gtt ccc tgc aac tgc aat tct ttt ggg tct aag tca ttc gac tgt Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys 965 970 975			2986

gaa gag agt gga caa tgt tgg tgc caa cct gga gtc aca ggg aag aaa	3034
Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys	
980 985 990 995	
tgt gac cgc tgt gcc cac ggc tat ttc aac ttc caa gaa gga ggc tgc	3082
Cys Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys	
1000 1005 1010	
aca gct tgt gaa tgt tct cat ctg ggt aat aat tgt gac cca aag act	3130
Thr Ala Cys Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr	
1015 1020 1025	
ggg cga tgc att tgc cca ccc aat acc att gga gag aaa tgt tct aaa	3178
Gly Arg Cys Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys	
1030 1035 1040	
tgt gca ccc aat acc tgg ggc cac agc att acc act ggt tgt aag gct	3226
Cys Ala Pro Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala	
1045 1050 1055	
tgt aac tgc agc aca gtg gga tcc ttg gat ttc caa tgc aat gta aat	3274
Cys Asn Cys Ser Thr Val Gly Ser Leu Asp Phe Gln Cys Asn Val Asn	
1060 1065 1070 1075	
aca ggc caa tgc aac tgt cat cca aaa ttc tct ggt gca aaa tgt aca	3322
Thr Gly Gln Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr	
1080 1085 1090	
gag tgc agt cga ggt cac tgg aac tac cct cgc tgc aat ctc tgt gac	3370
Glu Cys Ser Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp	
1095 1100 1105	
tgc ttc ctc cct ggg aca gat gcc aca acc tgt gat tca gag act aaa	3418
Cys Phe Leu Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser Glu Thr Lys	
1110 1115 1120	
aaa tgc tcc tgt agt gat caa act ggg cag tgc act tgt aag gtg aat	3466
Lys Cys Ser Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys Lys Val Asn	
1125 1130 1135	
gtg gaa ggc atc cac tgt gac aga tgc cgg cct ggc aaa ttc gga ctc	3514
Val Glu Gly Ile His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu	
1140 1145 1150 1155	
gat gcc aag aat cca ctt ggc tgc agc agc tgc tat tgc ttc ggc act	3562
Asp Ala Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr	
1160 1165 1170	
act acc cag tgc tct gaa gca aaa gga ctg atc cgg acg tgg gtg act	3610
Thr Thr Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr	
1175 1180 1185	
ctg aag gct gag cag acc att cta ccc ctg gta gat gag gct ctg cag	3658
Leu Lys Ala Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln	
1190 1195 1200	
cac acg acc acc aag ggc att gtt ttt caa cat cca gag att gtt gcc	3706
His Thr Thr Thr Lys Gly Ile Val Phe Gln His Pro Glu Ile Val Ala	
1205 1210 1215	

cac atg gac ctg atg aga gaa gat ctc cat ttg gaa cct ttt tat tgg	3754
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp	
1220 1225 1230 1235	
aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc	3802
Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly	
1240 1245 1250	
aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc	3850
Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe	
1255 1260 1265	
tct aca tat aat cct caa gtg atc att cga ggt ggg aca cct act cat	3898
Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His	
1270 1275 1280	
gct aga att atc gtc agg cat atg gct gct cct ctg att ggc caa ttg	3946
Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu	
1285 1290 1295	
aca agg cat gaa att gaa atg aca gag aaa gaa tgg aaa tat tat ggg	3994
Thr Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly	
1300 1305 1310 1315	
gat gat cct cga gtc cat aga act gtg acc cga gaa gac ttc ttg gat	4042
Asp Asp Pro Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp	
1320 1325 1330	
ata cta tat gat att cat tac att ctt atc aaa gct act tat gga aat	4090
Ile Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn	
1335 1340 1345	
ttc atg cga caa agc agg att tct gaa atc tca atg gag gta gct gaa	4138
Phe Met Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu	
1350 1355 1360	
caa gga cgt gga aca aca atg act cct cca gct gac ttg att gaa aaa	4186
Gln Gly Arg Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys	
1365 1370 1375	
tgt gat tgt ccc ctg ggc tat tct ggc ctg tcc tgt gag gca tgc ttg	4234
Cys Asp Cys Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu	
1380 1385 1390 1395	
ccg gga ttt tat cga ctg cgt tct caa cca ggt ggc cgc acc cct gga	4282
Pro Gly Phe Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly	
1400 1405 1410	
cca acc ctg ggc acc tgt gtt cca tgt caa tgt aat gga cac agc agc	4330
Pro Thr Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser	
1415 1420 1425	
ctg tgt gac cct gaa aca tcg ata tgc cag aat tgt caa cat cac act	4378
Leu Cys Asp Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr	
1430 1435 1440	
gct ggt gac ttc tgt gaa cga tgt gct ctt gga tac tat gga att gtc	4426
Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val	
1445 1450 1455	
aag gga ttg cca aat gac tgt cag caa tgt gcc tgc cct ctg att tct	4474

Lys Gly Leu Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser	
1460	1475
tcc agt aac aat ttc agc ccc tct tgt gtc gca gaa gga ctt gac gac	4522
Ser Ser Asn Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp	
1480	1490
tac cgc tgc acg gct tgt cca cgg gga tat gaa ggc cag tac tgt gaa	4570
Tyr Arg Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu	
1495	1505
agg tgt gcc cct ggc tat act ggc agt cca ggc aac cct gga ggc tcc	4618
Arg Cys Ala Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser	
1510	1520
tgc caa gaa tgt gag tgt gat ccc tat ggc tca ctg cct gtg ccc tgt	4666
Cys Gln Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys	
1525	1535
gac cct gtc aca gga ttc tgc acg tgc cga cct gga gcc acg gga agg	4714
Asp Pro Val Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg	
1540	1555
aag tgt gac ggc tgc aag cac tgg cat gca cgc gag ggc tgg gag tgt	4762
Lys Cys Asp Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys	
1560	1570
gtt ttt tgt gga gat gag tgc act ggc ctt ctt etc ggt gac ttg gct	4810
Val Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala	
1575	1585
cgc ctg gag cag atg gtc atg agc atc aac ctc act ggt ccg ctg cct	4858
Arg Leu Glu Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro	
1590	1600
gcg cca tat aaa atg ctg tat ggt ctt gaa aat atg act cag gag cta	4906
Ala Pro Tyr Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu	
1605	1615
aag cac ttg ctg tca cct cag cgg gcc cca gag agg ctt att cag ctg	4954
Lys His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu	
1620	1635
gca gag ggc aat ctg aat aca ctc gtg acc gaa atg aac gag ctg ctg	5002
Ala Glu Gly Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu	
1640	1650
acc agg gct acc aaa gtg aca gca gat ggc gag cag acc gga cag gat	5050
Thr Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp	
1655	1665
gct gag agg acc aac aca aga gca aag tcc ctg gga gaa ttc att aag	5098
Ala Glu Arg Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys	
1670	1680
gag ctt gcc cgg gat gca gaa gct gta aat gaa aaa gct ata aaa cta	5146
Glu Leu Ala Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu	
1685	1695
aat gaa act cta gga act cga gac gag gcc ttt gag aga aat ttg gaa	5194
Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu	

1700	1705	1710	1715	
ggg ctt cag aaa gag att gac cag atg att aaa gaa ctg agg agg aaa				5242
Gly Leu Gln Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys				
1720	1725	1730		
aat cta gag aca caa aag gaa att gct gaa gat gag ttg gta gct gca				5290
Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala				
1735	1740	1745		
gaa gcc ctt ctg aaa aaa gtg aag aag ctg ttt gga gag tcc cgg ggg				5338
Glu Ala Leu Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly				
1750	1755	1760		
gaa aat gaa gaa atg gag aag gat ctc cgg gaa aaa ctg gct gac tac				5386
Glu Asn Glu Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr				
1765	1770	1775		
aaa aac aaa gtt gat gat gct tgg gac ctt ttg aga gaa gcc aca gat				5434
Lys Asn Lys Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp				
1780	1785	1790	1795	
aaa atc aga gaa gct aat cgc cta ttt gca gta aat cag aaa aac atg				5482
Lys Ile Arg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met				
1800	1805	1810		
act gca ttg gag aaa aag aag gag gct gtt gag agc ggc aaa cga caa				5530
Thr Ala Leu Glu Lys Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln				
1815	1820	1825		
att gag aac act tta aaa gaa ggc aat gac ata ctc gat gaa gcc aac				5578
Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn				
1830	1835	1840		
cgt ctt gca gat gaa atc aac tcc atc ata gac tat gtt gaa gac atc				5626
Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile				
1845	1850	1855		
caa act aaa ttg cca cct atg tct gag gag ctt aat gat aaa ata gat				5674
Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp				
1860	1865	1870	1875	
gac ctc tcc caa gaa ata aag gac agg aag ctt gct gag aag gtg tcc				5722
Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser				
1880	1885	1890		
cag gct gag agc cac gca gct cag ttg aat gac tca tct gct gtc ctt				5770
Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu				
1895	1900	1905		
gat gga atc ctt gat gag gct aaa aac atc tcc ttc aat gcc act gca				5818
Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala				
1910	1915	1920		
gcc ttc aaa gct tac agc aat att aag gac tat att gat gaa gct gag				5866
Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu				
1925	1930	1935		
aaa gtt gcc aaa gaa gcc aaa gat ctt gca cat gaa gct aca aaa ctg				5914
Lys Val Ala Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu				
1940	1945	1950	1955	

gca aca ggt cct cgg ggt tta tta aag gaa gat gcc aaa ggc tgt ctt Ala Thr Gly Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu 1960 1965 1970	5962
cag aaa agc ttc agg att ctt aac gaa gcc aag aag tta gca aat gat Gln Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp 1975 1980 1985	6010
gta aaa gaa aat gaa gac cat cta aat ggc tta aaa acc agg ata gaa Val Lys Glu Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu 1990 1995 2000	6058
aat gct gat gct aga aat ggg gat ctc ttg aga act ttg aat gac act Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr 2005 2010 2015	6106
ttg gga aag tta tca gct att cca aat gat aca gct gct aaa ctg caa Leu Gly Lys Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln 2020 2025 2030 2035	6154
gct gtt aag gac aaa gcc aga caa gcc aac gac aca gct aaa gat gta Ala Val Lys Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val 2040 2045 2050	6202
ctg gca cag att aca gag ctc cac cag aac ctc gat ggc ctg aag aag Leu Ala Gln Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys 2055 2060 2065	6250
aat tac aat aaa cta gca gac agc gtc gcc aaa acg aat gct gtg gtt Asn Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val 2070 2075 2080	6298
aaa gat cct tcc aag aac aaa atc att gcc gat gca gat gcc act gtc Lys Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val 2085 2090 2095	6346
aaa aat tta gaa cag gaa gct gac cgg cta ata gat aaa ctc aaa ccc Lys Asn Leu Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro 2100 2105 2110 2115	6394
atc aag gaa ctt gag gat aac cta aag aaa aac atc tct gag ata aag Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys 2120 2125 2130	6442
gaa ttg ata aac caa gct cgg aaa caa gcc aat tct atc aaa gta tct Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser 2135 2140 2145	6490
gtg tct tca gga ggt gac tgc att cga aca tac aaa cca gaa atc aag Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys 2150 2155 2160	6538
aaa gga agt tac aat aat att gtt gtc aac gta aag aca gct gtt gct Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala 2165 2170 2175	6586
gat aac ctc ctc ttt tat ctt gga agt gcc aaa ttt att gac ttt ctg Asp Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu 2180 2185 2190 2195	6634

gct ata gaa atg cgt aaa ggc aaa gtc agc ttc ctc tgg gat gtt gga	6682
Ala Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp Asp Val Gly	
2200 2205 2210	
tct gga gtt gga cgt gta gag tac cca gat ttg act att gat gac tca	6730
Ser Gly Val Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser	
2215 2220 2225	
tat tgg tac cgt atc gta gca tca aga act ggg aga aat gga act att	6778
Tyr Trp Tyr Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile	
2230 2235 2240	
tct gtg aga gcc ctg gat gga ccc aaa gcc agc att gtg ccc agc aca	6826
Ser Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Ile Val Pro Ser Thr	
2245 2250 2255	
cac cat tcg acg tct cct cca ggg tac acg att cta gat gtg gat gca	6874
His His Ser Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala	
2260 2265 2270 2275	
aat gca atg ctg ttt gtt ggt ggc ctg act ggg aaa tta aag aag gct	6922
Asn Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Leu Lys Lys Ala	
2280 2285 2290	
gat gct gta cgt gtg att aca ttc act ggc tgc atg gga gaa aca tac	6970
Asp Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr	
2295 2300 2305	
ttt gac aac aaa cct ata ggt ttg tgg aat ttc cga gaa aaa gaa ggt	7018
Phe Asp Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly	
2310 2315 2320	
gac tgc aaa gga tgc act gtc agt cct cag gtg gaa gat agt gag ggg	7066
Asp Cys Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly	
2325 2330 2335	
act att caa ttt gat gga gaa ggt tat gca ttg gtc agc cgt ccc att	7114
Thr Ile Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile	
2340 2345 2350 2355	
cgc tgg tac ccc aac atc tcc act gtc atg ttc aag ttc aga aca ttt	7162
Arg Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe	
2360 2365 2370	
tct tcg agt gct ctt ctg atg tat ctt gcc aca cga gac ctg aga gat	7210
Ser Ser Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp	
2375 2380 2385	
ttc atg agt gtg gag ctc act gat ggg cac ata aaa gtc agt tac gat	7258
Phe Met Ser Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp	
2390 2395 2400	
ctg ggc tca gga atg gct tcc gtt gtc agc aat caa aac cat aat gat	7306
Leu Gly Ser Gly Met Ala Ser Val Val Ser Asn Gln Asn His Asn Asp	
2405 2410 2415	
ggg aaa tgg aaa tca ttc act ctg tca aga att caa aaa caa gcc aat	7354
Gly Lys Trp Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn	
2420 2425 2430 2435	
ata tca att gta gat ata gat act aat cag gag gag aat ata gca act	7402

Ile Ser Ile Val Asp Ile Asp Thr Asn Gln Glu Glu Asn Ile Ala Thr	
2440 2445 2450	
tgc tct tct gga aac aac ttt ggt ctt gac ttg aaa gca gat gac aaa	7450
Ser Ser Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys	
2455 2460 2465	
ata tat ttt ggt ggc ctg cca acg ctg aga aac ttg agt atg aaa gca	7498
Ile Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala	
2470 2475 2480	
agg cca gaa gta aat ctg aag aaa tat tcc ggc tgc ctc aaa gat att	7546
Arg Pro Glu Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile	
2485 2490 2495	
gaa att tca aga act ccg tac aat ata ctc agt agt ccc gat tat gtt	7594
Glu Ile Ser Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val	
2500 2505 2510 2515	
ggt gtt acc aaa gga tgt tcc ctg gag aat gtt tac aca gtt agc ttt	7642
Gly Val Thr Lys Gly Cys Ser Leu Glu Asn Val Tyr Thr Val Ser Phe	
2520 2525 2530	
cct aag cct ggt ttt gtg gag ctc tcc cct gtg cca att gat gta gga	7690
Pro Lys Pro Gly Phe Val Glu Leu Ser Pro Val Pro Ile Asp Val Gly	
2535 2540 2545	
aca gaa atc aac ctg tca ttc agc acc aag aat gag tcc ggc atc att	7738
Thr Glu Ile Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile	
2550 2555 2560	
ctt ttg gga agt gga ggg aca cca gca cca cct agg aga aaa cga agg	7786
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro Pro Arg Arg Lys Arg Arg	
2565 2570 2575	
cag act gga cag gcc tat tat gta ata ctc ctc aac agg ggc cgt ctg	7834
Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg Gly Arg Leu	
2580 2585 2590 2595	
gaa gtg cat ctc tcc aca ggg gca cga aca atg agg aaa att gtc atc	7882
Glu Val His Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile	
2600 2605 2610	
aga cca gag ccg aat ctg ttt cat gat gga aga gaa cat tcc gtt cat	7930
Arg Pro Glu Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His	
2615 2620 2625	
gta gag cga act aga ggc atc ttt aca gtt caa gtg gat gaa aac aga	7978
Val Glu Arg Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg	
2630 2635 2640	
aga tac atg caa aac ctg aca gtt gaa cag cct atc gaa gtt aaa aag	8026
Arg Tyr Met Gln Asn Leu Thr Val Glu Gln Pro Ile Glu Val Lys Lys	
2645 2650 2655	
ctt ttc gtt ggg ggt gct cca cct gaa ttt caa cct tcc cca ctc aga	8074
Leu Phe Val Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg	
2660 2665 2670 2675	
aat att cct cct ttt gaa ggc tgc ata tgg aat ctt gtt att aac tct	8122
Asn Ile Pro Pro Phe Glu Gly Cys Ile Trp Asn Leu Val Ile Asn Ser	

2680	2685	2690	
gtc ccc atg gac ttt gca agg cct gtg tcc ttc aaa aat gct gac att			8170
Val Pro Met Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile			
2695	2700	2705	
ggc cgc tgt gcc cat cag aaa ctc cgt gaa gat gaa gat gga gca gct			8218
Gly Arg Cys Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala Ala			
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cca gct gaa ata gtt atc cag cct gag cca gtt ccc acc cca gcc ttt			8266
Pro Ala Glu Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe			
2725	2730	2735	
cct acg ccc acc cca gtt ctg aca cat ggt cct tgt gct gca gaa tca			8314
Pro Thr Pro Thr Pro Val Leu Thr His Gly Pro Cys Ala Ala Glu Ser			
2740	2745	2750	2755
gaa cca gct ctt ttg ata ggg agc aag cag ttc ggg ctt tca aga aac			8362
Glu Pro Ala Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn			
2760	2765	2770	
agt cac att gca att gca ttt gat gac acc aaa gtt aaa aac cgt ctc			8410
Ser His Ile Ala Ile Ala Phe Asp Asp Thr Lys Val Lys Asn Arg Leu			
2775	2780	2785	
aca att gag ttg gaa gta aga acc gaa gct gaa tcc ggc ttg ctt ttt			8458
Thr Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe			
2790	2795	2800	
tac atg gct gcg atc aat cat gct gat ttt gca aca gtt cag ctg aga			8506
Tyr Met Ala Ala Ile Asn His Ala Asp Phe Ala Thr Val Gln Leu Arg			
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Asn Gly Leu Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His			
2820	2825	2830	2835
acc atg atc ccc acc aaa atc aat gat ggc cag tgg cac aag att aag			8602
Thr Met Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys			
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ata atg aga agt aag caa gaa gga att ctt tat gta gat ggg gct tcc			8650
Ile Met Arg Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser			
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aac aga acc atc agt ccc aaa aaa gcc gac atc ctg gat gtc gtg gga			8698
Asn Arg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly			
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Met Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile			
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Gly Pro Val Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met			
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gca gag gcc cct gcc gat ctg gaa caa ccc acc tcc agc ttc cat gtt			8842
Ala Glu Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val			
2920	2925	2930	

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 Gly Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe Asp Gly Thr
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 ggt ttt gcc aaa gca gtt ggt gga ttc aaa gtg gga ttg gac ctt ctt 8938
 Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu Leu
 2950 2955 2960
 gta gaa ttt gaa ttc gcg aca act aca acg act gga gtt ctt ctg ggg 8986
 Val Glu Phe Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly
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 Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu
 2980 2985 2990 2995
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 Lys Leu Met Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Val
 3000 3005 3010
 tat gat gct ggg gtt cca ggg cat ttg tgt gat gga caa tgg cat aaa 9130
 Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp Gly Gln Trp His Lys
 3015 3020 3025
 gtc act gcc aac aag atc aaa cac cgc att gag ctc aca gtc gat ggg 9178
 Val Thr Ala Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly
 3030 3035 3040
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 Asn Gln Val Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp
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 Thr Asn Asp Pro Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln
 3060 3065 3070 3075
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 Phe Gly Leu Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu
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 Lys Leu Thr Lys Gly Thr Ala Ser His Trp Arg Leu Ile Leu Pro Arg
 3095 3100 3105
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 Pro Trp Asn
 3110
 aaaataagtg taacccacagg aagagtcctgt caaaacaagt atatcaagta aaacaaacaa 9479
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 <211> 3110
 <212> PRT
 <213> Homo sapiens

<400> 6
 Met Pro Gly Ala Ala Gly Val Leu Leu Leu Leu Leu Leu Ser Gly Gly

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Ala His Gln Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser	35	40	45
Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu	50	55	60
Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn	65	70	75
Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg	85	90	95
His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser	100	105	110
Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu	115	120	125
Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala	130	135	140
Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp	145	150	155
Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys	165	170	175
Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala	180	185	190
Lys Asp Asp Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro	195	200	205
Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser	210	215	220
Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr	225	230	235
Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met	245	250	255
Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg	260	265	270
Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile	275	280	285
Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys	290	295	300
Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln	305	310	315
Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu	325	330	335

Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu
 340 345 350
 Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile
 355 360 365
 Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn
 370 375 380
 Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro
 385 390 395 400
 Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys
 405 410 415
 Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His
 420 425 430
 Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe
 435 440 445
 Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro
 450 455 460
 Asp Cys Lys Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp
 465 470 475 480
 Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp
 485 490 495
 Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp
 500 505 510
 Lys Gly Cys Asp Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln
 515 520 525
 Ser Ser Tyr Trp Thr Tyr Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr
 530 535 540
 Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Gln Asp Asp
 545 550 555 560
 Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln
 565 570 575
 Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly
 580 585 590
 Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr
 595 600 605
 Asp Leu Glu Glu Glu Glu Glu Asp Thr Glu Arg Val Leu Gln Leu Met
 610 615 620
 Ile Ile Leu Glu Gly Asn Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu
 625 630 635 640
 Val Tyr Leu His Pro Ser Glu Glu His Thr Asn Val Leu Leu Leu Lys
 645 650 655

Glu Glu Ser Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys
 660 665 670
 Glu Phe Met Thr Val Leu Ala Asn Leu Lys Arg Val Leu Leu Gln Ile
 675 680 685
 Thr Tyr Ser Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn
 690 695 700
 Leu Glu Ser Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala
 705 710 715 720
 Val Glu Val Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu
 725 730 735
 Ser Cys Trp Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly
 740 745 750
 Ile Cys Glu Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp
 755 760 765
 Val Thr Gly Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr
 770 775 780
 Cys Asp Lys Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr
 785 790 795 800
 Ser Glu Asp Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn
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 820 825 830
 Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala
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 Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro
 850 855 860
 Cys Gln Cys Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp
 865 870 875 880
 Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg
 885 890 895
 Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala
 900 905 910
 Lys Asn Cys Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu
 915 920 925
 Val Cys His Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln
 930 935 940
 Gly Gln Arg Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser
 945 950 955 960
 Ala Arg Gly Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser
 965 970 975
 Phe Asp Cys Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr

980	985	990
Gly Lys Lys Cys Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu 995 1000 1005		
Gly Gly Cys Thr Ala Cys Glu Cys Ser His Leu Gly Asn Asn Cys Asp 1010 1015 1020		
Pro Lys Thr Gly Arg Cys Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys 025 1030 1035 1040		
Cys Ser Lys Cys Ala Pro Asn Thr Trp Gly His Ser Ile Thr Thr Gly 1045 1050 1055		
Cys Lys Ala Cys Asn Cys Ser Thr Val Gly Ser Leu Asp Phe Gln Cys 1060 1065 1070		
Asn Val Asn Thr Gly Gln Cys Asn Cys His Pro Lys Phe Ser Gly Ala 1075 1080 1085		
Lys Cys Thr Glu Cys Ser Arg Gly His Trp Asn Tyr Pro Arg Cys Asn 1090 1095 1100		
Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser 105 1110 1115 1120		
Glu Thr Lys Lys Cys Ser Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys 1125 1130 1135		
Lys Val Asn Val Glu Gly Ile His Cys Asp Arg Cys Arg Pro Gly Lys 1140 1145 1150		
Phe Gly Leu Asp Ala Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys 1155 1160 1165		
Phe Gly Thr Thr Thr Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr 1170 1175 1180		
Trp Val Thr Leu Lys Ala Glu Gln Thr Ile Leu Pro Leu Val Asp Glu 185 1190 1195 1200		
Ala Leu Gln His Thr Thr Thr Lys Gly Ile Val Phe Gln His Pro Glu 1205 1210 1215		
Ile Val Ala His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro 1220 1225 1230		
Phe Tyr Trp Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala 1235 1240 1245		
Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu 1250 1255 1260		
Thr Gly Phe Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr 265 1270 1275 1280		
Pro Thr His Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile 1285 1290 1295		
Gly Gln Leu Thr Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys 1300 1305 1310		

Tyr Tyr Gly Asp Asp Pro Arg Val His Arg Thr Val Thr Arg Glu Asp
 1315 1320 1325
 Phe Leu Asp Ile Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr
 1330 1335 1340
 Tyr Gly Asn Phe Met Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu
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 Val Ala Glu Gln Gly Arg Gly Thr Thr Met Thr Pro Pro Ala Asp Leu
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 Ile Glu Lys Cys Asp Cys Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu
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 1395 1400 1405
 Thr Pro Gly Pro Thr Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly
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 His Ser Ser Leu Cys Asp Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln
 425 1430 1435 1440
 His His Thr Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr
 1445 1450 1455
 Gly Ile Val Lys Gly Leu Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro
 1460 1465 1470
 Leu Ile Ser Ser Ser Asn Asn Phe Ser Pro Ser Cys Val Ala Glu Gly
 1475 1480 1485
 Leu Asp Asp Tyr Arg Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln
 1490 1495 1500
 Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro
 505 1510 1515 1520
 Gly Gly Ser Cys Gln Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro
 1525 1530 1535
 Val Pro Cys Asp Pro Val Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala
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 Thr Gly Arg Lys Cys Asp Gly Cys Lys His Trp His Ala Arg Glu Gly
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 Trp Glu Cys Val Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly
 1570 1575 1580
 Asp Leu Ala Arg Leu Glu Gln Met Val Met Ser Ile Asn Leu Thr Gly
 585 1590 1595 1600
 Pro Leu Pro Ala Pro Tyr Lys Met Leu Tyr Gly Leu Glu Asn Met Thr
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 Gln Glu Leu Lys His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu
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Ile Gln Leu Ala Glu Gly Asn Leu Asn Thr Leu Val Thr Glu Met Asn
 1635 1640 1645
 Glu Leu Leu Thr Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr
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 Gly Gln Asp Ala Glu Arg Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu
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 Phe Ile Lys Glu Leu Ala Arg Asp Ala Glu Ala Val Asn Glu Lys Ala
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 Ile Lys Leu Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg
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 Asn Leu Glu Gly Leu Gln Lys Glu Ile Asp Gln Met Ile Lys Glu Leu
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 Arg Arg Lys Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu
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 Val Ala Ala Glu Ala Leu Lys Lys Val Lys Lys Leu Phe Gly Glu
 745 1750 1755 1760
 Ser Arg Gly Glu Asn Glu Glu Met Glu Lys Asp Leu Arg Glu Lys Leu
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 1780 1785 1790
 Ala Thr Asp Lys Ile Arg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln
 1795 1800 1805
 Lys Asn Met Thr Ala Leu Glu Lys Lys Lys Glu Ala Val Glu Ser Gly
 1810 1815 1820
 Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp
 825 1830 1835 1840
 Glu Ala Asn Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val
 1845 1850 1855
 Glu Asp Ile Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp
 1860 1865 1870
 Lys Ile Asp Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu
 1875 1880 1885
 Lys Val Ser Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser
 1890 1895 1900
 Ala Val Leu Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn
 905 1910 1915 1920
 Ala Thr Ala Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp
 1925 1930 1935
 Glu Ala Glu Lys Val Ala Lys Glu Ala Lys Asp Leu Ala His Glu Ala
 1940 1945 1950
 Thr Lys Leu Ala Thr Gly Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys

1955	1960	1965
Gly Cys Leu Gln Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu 1970	1975	1980
Ala Asn Asp Val Lys Glu Asn Glu Asp His Leu Asn Gly Leu Lys Thr 985	1990	1995 2000
Arg Ile Glu Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu 2005	2010	2015
Asn Asp Thr Leu Gly Lys Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala 2020	2025	2030
Lys Leu Gln Ala Val Lys Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala 2035	2040	2045
Lys Asp Val Leu Ala Gln Ile Thr Glu Leu His Gln Asn Leu Asp Gly 2050	2055	2060
Leu Lys Lys Asn Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn 065	2070	2075 2080
Ala Val Val Lys Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp 2085	2090	2095
Ala Thr Val Lys Asn Leu Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys 2100	2105	2110
Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser 2115	2120	2125
Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile 2130	2135	2140
Lys Val Ser Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro 145	2150	2155 2160
Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr 2165	2170	2175
Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile 2180	2185	2190
Asp Phe Leu Ala Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp 2195	2200	2205
Asp Val Gly Ser Gly Val Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile 2210	2215	2220
Asp Asp Ser Tyr Trp Tyr Arg Ile Val Ala Ser Arg Thr Gly Arg Asn 225	2230	2235 2240
Gly Thr Ile Ser Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Ile Val 2245	2250	2255
Pro Ser Thr His His Ser Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp 2260	2265	2270
Val Asp Ala Asn Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Leu 2275	2280	2285

Lys Lys Ala Asp Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly
 2290 2295 2300
 Glu Thr Tyr Phe Asp Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu
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 Lys Glu Gly Asp Cys Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp
 2325 2330 2335
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 Arg Pro Ile Arg Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe
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 Arg Thr Phe Ser Ser Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp
 2370 2375 2380
 Leu Arg Asp Phe Met Ser Val Glu Leu Thr Asp Gly His Ile Lys Val
 385 2390 2395 2400
 Ser Tyr Asp Leu Gly Ser Gly Met Ala Ser Val Val Ser Asn Gln Asn
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 2595 2600 2605

Ile Val Ile Arg Pro Glu Pro Asn Leu Phe His Asp Gly Arg Glu His
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 2645 2650 2655
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 Pro Leu Arg Asn Ile Pro Pro Phe Glu Gly Cys Ile Trp Asn Leu Val
 2675 2680 2685
 Ile Asn Ser Val Pro Met Asp Phe Ala Arg Pro Val Ser Phe Lys Asn
 2690 2695 2700
 Ala Asp Ile Gly Arg Cys Ala His Gln Lys Leu Arg Glu Asp Glu Asp
 705 2710 2715 2720
 Gly Ala Ala Pro Ala Glu Ile Val Ile Gln Pro Glu Pro Val Pro Thr
 2725 2730 2735
 Pro Ala Phe Pro Thr Pro Thr Pro Val Leu Thr His Gly Pro Cys Ala
 2740 2745 2750
 Ala Glu Ser Glu Pro Ala Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu
 2755 2760 2765
 Ser Arg Asn Ser His Ile Ala Ile Ala Phe Asp Asp Thr Lys Val Lys
 2770 2775 2780
 Asn Arg Leu Thr Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly
 785 2790 2795 2800
 Leu Leu Phe Tyr Met Ala Ala Ile Asn His Ala Asp Phe Ala Thr Val
 2805 2810 2815
 Gln Leu Arg Asn Gly Leu Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly
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 Asp Thr His Thr Met Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His
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 Lys Ile Lys Ile Met Arg Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp
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 Gly Ala Ser Asn Arg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp
 865 2870 2875 2880
 Val Val Gly Met Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr
 2885 2890 2895
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 Leu His Met Ala Glu Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser
 2915 2920 2925
 Phe His Val Gly Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe

69

aat caa aac agc agc aat cca aac cag aga cac ccg att aca aat gct	240
Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile Thr Asn Ala	
65 70 75 80	
att gat gga aag aac act tgg tgg cag agt ccc agt att aag aat gga	288
Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly	
85 90 95	
atc gaa tac cat tat gtg aca att aca ctg gat tta cag cag gtg ttc	336
Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe	
100 105 110	
cag atc gcg tat gtg att gtg aag gca gct aac tcc ccc cgg cct gga	384
Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly	
115 120 125	
aac tgg att ttg gaa cgc tct ctt gat gat gtt gaa tac aag ccc tgg	432
Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp	
130 135 140	
cag tat cat gct gtg aca gac acg gag tgc cta acg ctt tac aat att	480
Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile	
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Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile	
165 170 175	
tgc act tca ttt tac tcc aag ata cac ccc tta gaa aat gga gag att	576
Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile	
180 185 190	
cac atc tct tta atc aat ggg aga cca agt gcc gat gat cct tct cca	624
His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro	
195 200 205	
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Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln	
210 215 220	
agg atc cgc aca ctg aat gct gac ttg atg atg ttt gct cac aaa gac	720
Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp	
225 230 235 240	
cca aga gaa att gac ccc att gtc acc aga aga tat tac tac tcg gtc	768
Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val	
245 250 255	
aag gat att tca gtt gga ggg atg tgc atc tgc tat ggt cat gcc agg	816
Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg	
260 265 270	
gct tgt cca ctt gat cca gcg aca aat aaa tct cgc tgt gag tgt gag	864
Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu	
275 280 285	
cat aac aca tgt ggc gat agc tgt gat cag tgc tgt cca gga ttc cat	912
His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His	
290 295 300	

cag aaa ccc tgg aga gct gga act ttt cta act aaa act gaa tgt gaa	960
Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu	
305 310 315 320	
gca tgc aat tgt cat gga aaa gct gaa gaa tgc tat tat gat gaa aat	1008
Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn	
325 330 335	
gtt gcc aga aga aat ctg agt ttg aat ata cgt gga aag tac att gga	1056
Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly	
340 345 350	
ggg ggt gtc tgc att aat tgt acc caa aac act gct ggt ata aac tgc	1104
Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys	
355 360 365	
gag aca tgt aca gat ggc ttc ttc aga ccc aaa ggg gta tct cca aat	1152
Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn	
370 375 380	
tat cca agg cca tgc cag cca tgt cat tgc gat cca att ggt tcc tta	1200
Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu	
385 390 395 400	
aat gaa gtc tgt gtc aag gat gag aaa cat gct cga cga ggt ttg gca	1248
Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala	
405 410 415	
cct gga tcc tgt cat tgc aaa act ggt ttt gga ggt gtg agc tgt gat	1296
Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp	
420 425 430	
cgg tgt gcc agg ggc tac act ggc tac ccg gac tgc aaa gcc tgt aac	1344
Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn	
435 440 445	
tgc agt ggg tta ggg agc aaa aat gag gat cct tgt ttt ggc ccc tgt	1392
Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys	
450 455 460	
atc tgc aag gaa aat gtt gaa gga gga gac tgt agt cgt tgc aaa tcc	1440
Ile Cys Lys Glu Asn Val Glu Gly Gly Asp Cys Ser Arg Cys Lys Ser	
465 470 475 480	
ggc ttc ttc aat ttg caa gag gat aat tgg aaa ggc tgc gat gag tgt	1488
Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp Lys Gly Cys Asp Glu Cys	
485 490 495	
ttc tgt tca ggg gtt tca aac aga tgt cag agt tcc tac tgg acc tat	1536
Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr	
500 505 510	
ggc aaa ata caa gat atg agt ggc tgg tat ctg act gac ctt cct ggc	1584
Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly	
515 520 525	
cgc att cga gtg gct ccc cag cag gac gac ttg gac tca cct cag cag	1632
Arg Ile Arg Val Ala Pro Gln Gln Asp Asp Leu Asp Ser Pro Gln Gln	
530 535 540	
atc agc atc agt aac gcg gag gcc cgg caa gcc ctg ccg cac agc tac	1680

Ile	Ser	Ile	Ser	Asn	Ala	Glu	Ala	Arg	Gln	Ala	Leu	Pro	His	Ser	Tyr	
545					550					555					560	
tac	tgg	agc	gcg	ccg	gct	ccc	tat	ctg	gga	aac	aaa	ctc	cca	gca	gta	1728
Tyr	Trp	Ser	Ala	Pro	Ala	Pro	Tyr	Leu	Gly	Asn	Lys	Leu	Pro	Ala	Val	
				565				570						575		
gga	gga	cag	ttg	aca	ttt	acc	ata	tca	tat	gac	ctt	gaa	gaa	gag	gaa	1776
Gly	Gly	Gln	Leu	Thr	Phe	Thr	Ile	Ser	Tyr	Asp	Leu	Glu	Glu	Glu	Glu	
			580					585						590		
gaa	gat	aca	gaa	cgt	gtt	ctc	cag	ctt	atg	att	atc	tta	gag	ggg	aat	1824
Glu	Asp	Thr	Glu	Arg	Val	Leu	Gln	Leu	Met	Ile	Ile	Leu	Glu	Gly	Asn	
			595				600					605				
gac	ttg	agc	atc	agc	aca	gcc	caa	gat	gag	gtg	tac	ctg	cac	cca	tct	1872
Asp	Leu	Ser	Ile	Ser	Thr	Ala	Gln	Asp	Glu	Val	Tyr	Leu	His	Pro	Ser	
	610					615					620					
gaa	gaa	cat	act	aat	gta	ttg	tta	ctt	aaa	gaa	gaa	tca	ttt	acc	ata	1920
Glu	Glu	His	Thr	Asn	Val	Leu	Leu	Leu	Lys	Glu	Glu	Ser	Phe	Thr	Ile	
	625				630				635						640	
cat	ggc	aca	cat	ttt	cca	gtc	cgt	aga	aag	gaa	ttt	atg	aca	gtg	ctt	1968
His	Gly	Thr	His	Phe	Pro	Val	Arg	Arg	Lys	Glu	Phe	Met	Thr	Val	Leu	
				645				650						655		
gcg	aat	ttg	aag	aga	gtc	ctc	cta	caa	atc	aca	tac	agc	ttt	ggg	atg	2016
Ala	Asn	Leu	Lys	Arg	Val	Leu	Leu	Gln	Ile	Thr	Tyr	Ser	Phe	Gly	Met	
			660					665						670		
gat	gcc	atc	ttc	agg	ttg	agc	tct	gtt	aac	ctt	gaa	tcc	gct	gtc	tcc	2064
Asp	Ala	Ile	Phe	Arg	Leu	Ser	Ser	Val	Asn	Leu	Glu	Ser	Ala	Val	Ser	
		675					680						685			
tat	cct	act	gat	gga	agc	att	gca	gca	gct	gta	gaa	gtg	tgt	cag	tgc	2112
Tyr	Pro	Thr	Asp	Gly	Ser	Ile	Ala	Ala	Ala	Val	Glu	Val	Cys	Gln	Cys	
		690				695					700					
cca	cca	ggg	tat	act	ggc	tcc	tct	tgt	gaa	tct	tgt	tgg	cct	agg	cac	2160
Pro	Pro	Gly	Tyr	Thr	Gly	Ser	Ser	Cys	Glu	Ser	Cys	Trp	Pro	Arg	His	
		705				710				715					720	
agg	cga	gtt	aac	ggc	act	att	ttt	ggg	ggc	atc	tgt	gag	cca	tgt	cag	2208
Arg	Arg	Val	Asn	Gly	Thr	Ile	Phe	Gly	Gly	Ile	Cys	Glu	Pro	Cys	Gln	
				725					730						735	
tgc	ttt	ggg	cat	gcg	gag	tcc	tgt	gat	gac	gtc	act	gga	gaa	tgc	ctg	2256
Cys	Phe	Gly	His	Ala	Glu	Ser	Cys	Asp	Asp	Val	Thr	Gly	Glu	Cys	Leu	
			740					745						750		
aac	tgt	aag	gat	cac	aca	ggg	ggc	cca	tat	tgt	gat	aaa	tgt	ctt	cct	2304
Asn	Cys	Lys	Asp	His	Thr	Gly	Gly	Pro	Tyr	Cys	Asp	Lys	Cys	Leu	Pro	
		755					760									
ggg	ttc	tat	ggc	gag	cct	act	aaa	gga	acc	tct	gaa	gac	tgt	caa	ccc	2352
Gly	Phe	Tyr	Gly	Glu	Pro	Thr	Lys	Gly	Thr	Ser	Glu	Asp	Cys	Gln	Pro	
		770				775										
tgt	gcc	tgt	cca	ctc	aat	atc	cca	tcc	aat	aac	ttt	agc	cca	acg	tgc	2400
Cys	Ala	Cys	Pro	Leu	Asn	Ile	Pro	Ser	Asn	Asn	Phe	Ser	Pro	Thr	Cys	

785	790	795	800	
cat tta gac cgg agt ctt gga ttg atc tgt gat gga tgc cct gtc ggg	2448			
His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly				
805	810	815		
tac aca gga cca cgc tgt gag agg tgt gca gaa ggc tat ttt gga caa	2496			
Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln				
820	825	830		
ccc tct gta cct gga gga tca tgt cag cca tgc caa tgc aat gac aac	2544			
Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn				
835	840	845		
ctt gac ttc tcc atc cct ggc agc tgt gac agc ttg tct ggc tcc tgt	2592			
Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys				
850	855	860		
ctg ata tgt aaa cca ggt aca aca ggc cgg tac tgt gag ctc tgt gct	2640			
Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala				
865	870	875	880	
gat gga tat ttt gga gat gca gtt gat gcg aag aac tgt cag ccc tgt	2688			
Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys				
885	890	895		
cgc tgt aat gcc ggt ggc tct ttc tct gag gtt tgc cac agt caa act	2736			
Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr				
900	905	910		
gga cag tgt gag tgc aga gcc aac gtt cag ggt cag aga tgt gac aaa	2784			
Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys				
915	920	925		
tgc aag gct ggg acc ttt ggc cta caa tca gca agg ggc tgt gtt ccc	2832			
Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro				
930	935	940		
tgc aac tgc aat tct ttt ggg tct aag tca ttc gac tgt gaa gag agt	2880			
Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Glu Ser				
945	950	955	960	
gga caa tgt tgg tgc caa cct gga gtc aca ggg aag aaa tgt gac cgc	2928			
Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg				
965	970	975		
tgt gcc cac ggc tat ttc aac ttc caa gaa gga ggc tgc aca gct tgt	2976			
Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys				
980	985	990		
gaa tgt tct cat ctg ggt aat aat tgt gac cca aag act ggg cga tgc	3024			
Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys				
995	1000	1005		
att tgc cca ccc aat acc att gga gag aaa tgt tct aaa tgt gca ccc	3072			
Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro				
1010	1015	1020		
aat acc tgg ggc cac agc att acc act ggt tgt aag gct tgt aac tgc	3120			
Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala Cys Asn Cys				
1025	1030	1035	1040	

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agc aca gtg gga tcc ttg gat ttc caa tgc aat gta aat aca ggc caa 3168
Ser Thr Val Gly Ser Leu Asp Phe Gln Cys Asn Val Asn Thr Gly Gln
1045 1050 1055

tgc aac tgt cat cca aaa ttc tct ggt gca aaa tgt aca gag tgc agt 3216
Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr Glu Cys Ser
1060 1065 1070

cga ggt cac tgg aac tac cct cgc tgc aat ctc tgt gac tgc ttc ctc 3264
Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp Cys Phe Leu
1075 1080 1085

cct ggg aca gat gcc aca acc tgt gat tca gag act aaa aaa tgc tcc 3312
Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser Glu Thr Lys Lys Cys Ser
1090 1095 1100

tgt agt gat caa act ggg cag tgc act tgt aag gtg aat gtg gaa ggc 3360
Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys Lys Val Asn Val Glu Gly
1105 1110 1115 1120

atc cac tgt gac aga tgc cgg cct ggc aaa ttc gga ctc gat gcc aag 3408
Ile His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys
1125 1130 1135

aat cca ctt ggc tgc agc agc tgc tat tgc ttc ggc act act acc cag 3456
Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr Thr Thr Gln
1140 1145 1150

tgc tct gaa gca aaa gga ctg atc cgg acg tgg gtg act ctg aag gct 3504
Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Lys Ala
1155 1160 1165

gag cag acc att cta ccc ctg gta gat gag gct ctg cag cac acg acc 3552
Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr
1170 1175 1180

acc aag ggc att gtt ttt caa cat cca gag att gtt gcc cac atg gac 3600
Thr Lys Gly Ile Val Phe Gln His Pro Glu Ile Val Ala His Met Asp
1185 1190 1195 1200

ctg atg aga gaa gat ctc cat ttg gaa cct ttt tat tgg aaa ctt cca 3648
Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro
1205 1210 1215

gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc aaa ctc aag 3696
Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys
1220 1225 1230

tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc tct aca tat 3744
Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe Ser Thr Tyr
1235 1240 1245

aat cct caa gtg atc att cga ggt ggg aca cct act cat gct aga att 3792
Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile
1250 1255 1260

atc gtc agg cat atg gct gct cct ctg att ggc caa ttg aca agg cat 3840
Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His
1265 1270 1275 1280

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gaa att gaa atg aca gag aaa gaa tgg aaa tat tat ggg gat gat cct Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro 1285 1290 1295	3888
cga gtc cat aga act gtg acc cga gaa gac ttc ttg gat ata cta tat Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr 1300 1305 1310	3936
gat att cat tac att ctt atc aaa gct act tat gga aat ttc atg cga Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Phe Met Arg 1315 1320 1325	3984
caa agc agg att tct gaa atc tca atg gag gta gct gaa caa gga cgt Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Gln Gly Arg 1330 1335 1340	4032
gga aca aca atg act cct cca gct gac ttg att gaa aaa tgt gat tgt Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys Cys Asp Cys 1345 1350 1355 1360	4080
ccc ctg ggc tat tct ggc ctg tcc tgt gag gca tgc ttg ccg gga ttt Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu Pro Gly Phe 1365 1370 1375	4128
tat cga ctg cgt tct caa cca ggt ggc cgc acc cct gga cca acc ctg Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu 1380 1385 1390	4176
ggc acc tgt gtt cca tgt caa tgt aat gga cac agc agc ctg tgt gac Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser Leu Cys Asp 1395 1400 1405	4224
cct gaa aca tcg ata tgc cag aat tgt caa cat cac act gct ggt gac Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr Ala Gly Asp 1410 1415 1420	4272
ttc tgt gaa cga tgt gct ctt gga tac tat gga att gtc aag gga ttg Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val Lys Gly Leu 1425 1430 1435 1440	4320
cca aat gac tgt cag caa tgt gcc tgc cct ctg att tct tcc agt aac Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser Ser Ser Asn 1445 1450 1455	4368
aat ttc agc ccc tct tgt gtc gca gaa gga ctt gac gac tac cgc tgc Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp Tyr Arg Cys 1460 1465 1470	4416
acg gct tgt cca cgg gga tat gaa ggc cag tac tgt gaa agg tgt gcc Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala 1475 1480 1485	4464
cct ggc tat act ggc agt cca ggc aac cct gga ggc tcc tgc caa gaa Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser Cys Gln Glu 1490 1495 1500	4512
tgt gag tgt gat ccc tat ggc tca ctg cct gtg ccc tgt gac cct gtc Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Pro Val 1505 1510 1515 1520	4560
aca gga ttc tgc acg tgc cga cct gga gcc acg gga agg aag tgt gac	4608

Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp	
1525 1530 1535	
ggc tgc aag cac tgg cat gca cgc gag ggc tgg gag tgt gtt ttt tgt	4656
Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys Val Phe Cys	
1540 1545 1550	
gga gat gag tgc act ggc ctt ctt ctc ggt gac ttg gct cgc ctg gag	4704
Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala Arg Leu Glu	
1555 1560 1565	
cag atg gtc atg agc atc aac ctc act ggt ccg ctg cct gcg cca tat	4752
Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr	
1570 1575 1580	
aaa atg ctg tat ggt ctt gaa aat atg act cag gag cta aag cac ttg	4800
Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu Lys His Leu	
1585 1590 1595 1600	
ctg tca cct cag cgg gcc cca gag agg ctt att cag ctg gca gag ggc	4848
Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly	
1605 1610 1615	
aat ctg aat aca ctc gtg acc gaa atg aac gag ctg ctg acc agg gct	4896
Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu Thr Arg Ala	
1620 1625 1630	
acc aaa gtg aca gca gat ggc gag cag acc gga cag gat gct gag agg	4944
Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg	
1635 1640 1645	
acc aac aca aga gca aag tcc ctg gga gaa ttc att aag gag ctt gcc	4992
Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys Glu Leu Ala	
1650 1655 1660	
cgg gat gca gaa gct gta aat gaa aaa gct ata aaa cta aat gaa act	5040
Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu Asn Glu Thr	
1665 1670 1675 1680	
cta gga act cga gac gag gcc ttt gag aga aat ttg gaa ggg ctt cag	5088
Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu Gly Leu Gln	
1685 1690 1695	
aaa gag att gac cag atg att aaa gaa ctg agg agg aaa aat cta gag	5136
Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys Asn Leu Glu	
1700 1705 1710	
aca caa aag gaa att gct gaa gat gag ttg gta gct gca gaa gcc ctt	5184
Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala Glu Ala Leu	
1715 1720 1725	
ctg aaa aaa gtg aag aag ctg ttt gga gag tcc cgg ggg gaa aat gaa	5232
Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly Glu Asn Glu	
1730 1735 1740	
gaa atg gag aag gat ctc cgg gaa aaa ctg gct gac tac aaa aac aaa	5280
Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys	
1745 1750 1755 1760	
gtt gat gat gct tgg gac ctt ttg aga gaa gcc aca gat aaa atc aga	5328
Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Ile Arg	

1765	1770	1775	
gaa gct aat cgc cta ttt gca gta aat cag aaa aac atg act gca ttg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu 1780 1785 1790			5376
gag aaa aag aag gag gct gtt gag agc ggc aaa cga caa att gag aac Glu Lys Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn 1795 1800 1805			5424
act tta aaa gaa ggc aat gac ata ctc gat gaa gcc aac cgt ctt gca Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala 1810 1815 1820			5472
gat gaa atc aac tcc atc ata gac tat gtt gaa gac atc caa act aaa Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys 1825 1830 1835 1840			5520
ttg cca cct atg tct gag gag ctt aat gat aaa ata gat gac ctc tcc Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser 1845 1850 1855			5568
caa gaa ata aag gac agg aag ctt gct gag aag gtg tcc cag gct gag Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu 1860 1865 1870			5616
agc cac gca gct cag ttg aat gac tca tct gct gtc ctt gat gga atc Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile 1875 1880 1885			5664
ctt gat gag gct aaa aac atc tcc ttc aat gcc act gca gcc ttc aaa Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys 1890 1895 1900			5712
gct tac agc aat att aag gac tat att gat gaa gct gag aaa gtt gcc Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala 1905 1910 1915 1920			5760
aaa gaa gcc aaa gat ctt gca cat gaa gct aca aaa ctg gca aca ggt Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly 1925 1930 1935			5808
cct cgg ggt tta tta aag gaa gat gcc aaa ggc tgt ctt cag aaa agc Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser 1940 1945 1950			5856
ttc agg att ctt aac gaa gcc aag aag tta gca aat gat gta aaa gaa Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu 1955 1960 1965			5904
aat gaa gac cat cta aat ggc tta aaa acc agg ata gaa aat gct gat Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu Asn Ala Asp 1970 1975 1980			5952
gct aga aat ggg gat ctc ttg aga act ttg aat gac act ttg gga aag Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys 1985 1990 1995 2000			6000
tta tca gct att cca aat gat aca gct gct aaa ctg caa gct gtt aag Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys 2005 2010 2015			6048

gac aaa gcc aga caa gcc aac gac aca gct aaa gat gta ctg gca cag Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln 2020 2025 2030	6096
att aca gag ctc cac cag aac ctc gat ggc ctg aag aag aat tac aat Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn 2035 2040 2045	6144
aaa cta gca gac agc gtc gcc aaa acg aat gct gtg gtt aaa gat cct Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro 2050 2055 2060	6192
tcc aag aac aaa atc att gcc gat gca gat gcc act gtc aaa aat tta Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val Lys Asn Leu 2065 2070 2075 2080	6240
gaa cag gaa gct gac cgg cta ata gat aaa ctc aaa ccc atc aag gaa Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu 2085 2090 2095	6288
ctt gag gat aac cta aag aaa aac atc tct gag ata aag gaa ttg ata Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile 2100 2105 2110	6336
aac caa gct cgg aaa caa gcc aat tct atc aaa gta tct gtg tct tca Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser 2115 2120 2125	6384
gga ggt gac tgc att cga aca tac aaa cca gaa atc aag aaa gga agt Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys Lys Gly Ser 2130 2135 2140	6432
tac aat aat att gtt gtc aac gta aag aca gct gtt gct gat aac ctc Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala Asp Asn Leu 2145 2150 2155 2160	6480
ctc ttt tat ctt gga agt gcc aaa ttt att gac ttt ctg gct ata gaa Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile Glu 2165 2170 2175	6528
atg cgt aaa ggc aaa gtc agc ttc ctc tgg gat gtt gga tct gga gtt Met Arg Lys Gly Lys Val Ser Phe Leu Trp Asp Val Gly Ser Gly Val 2180 2185 2190	6576
gga cgt gta gag tac cca gat ttg act att gat gac tca tat tgg tac Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195 2200 2205	6624
cgt atc gta gca tca aga act ggg aga aat gga act att tct gtg aga Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile Ser Val Arg 2210 2215 2220	6672
gcc ctg gat gga ccc aaa gcc agc att gtg ccc agc aca cac cat tcc Ala Leu Asp Gly Pro Lys Ala Ser Ile Val Pro Ser Thr His His Ser 2225 2230 2235 2240	6720
acg tct cct cca ggg tac acg att cta gat gtg gat gca aat gca atg Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala Met 2245 2250 2255	6768

ctg ttt gtt ggt ggc ctg act ggg aaa tta aag aag gct gat gct gta	6816
Leu Phe Val Gly Gly Leu Thr Gly Lys Leu Lys Lys Ala Asp Ala Val	
2260 2265 2270	
cg t gtg att aca ttc act ggc tgc atg gga gaa aca tac ttt gac aac	6864
Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn	
2275 2280 2285	
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Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys	
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Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln	
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Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr	
2325 2330 2335	
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Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser	
2340 2345 2350	
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Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp Phe Met Ser	
2355 2360 2365	
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Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser	
2370 2375 2380	
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Gly Met Ala Ser Val Val Ser Asn Gln Asn His Asn Asp Gly Lys Trp	
2385 2390 2395 2400	
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Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile	
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gta gat ata gat act aat cag gag gag aat ata gca act tgc tct tct	7296
Val Asp Ile Asp Thr Asn Gln Glu Glu Asn Ile Ala Thr Ser Ser Ser	
2420 2425 2430	
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Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe	
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Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu	
2450 2455 2460	
gta aat ctg aag aaa tat tcc ggc tgc ctc aaa gat att gaa att tca	7440
Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile Ser	
2465 2470 2475 2480	
aga act ccg tac aat ata ctc agt agt ccc gat tat gtt ggt gtt acc	7488
Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr	
2485 2490 2495	
aaa gga tgt tcc ctg gag aat gtt tac aca gtt agc ttt cct aag cct	7536

Lys Gly Cys Ser Leu Glu Asn Val Tyr Thr Val Ser Phe Pro Lys Pro	
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Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile Leu Leu Gly	
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agt gga ggg aca cca gca cca cct agg aga aaa cga agg cag act gga	7680
Ser Gly Gly Thr Pro Ala Pro Pro Arg Arg Lys Arg Arg Gln Thr Gly	
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cag gcc tat tat gta ata ctc ctc aac agg ggc cgt ctg gaa gtg cat	7728
Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg Gly Arg Leu Glu Val His	
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Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile Arg Pro Glu	
2580 2585 2590	
ccg aat ctg ttt cat gat gga aga gaa cat tcc gtt cat gta gag cga	7824
Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val Glu Arg	
2595 2600 2605	
act aga ggc atc ttt aca gtt caa gtg gat gaa aac aga aga tac atg	7872
Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg Arg Tyr Met	
2610 2615 2620	
caa aac ctg aca gtt gaa cag cct atc gaa gtt aaa aag ctt ttc gtt	7920
Gln Asn Leu Thr Val Glu Gln Pro Ile Glu Val Lys Lys Leu Phe Val	
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Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile Pro	
2645 2650 2655	
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Pro Phe Glu Gly Cys Ile Trp Asn Leu Val Ile Asn Ser Val Pro Met	
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Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile Gly Arg Cys	
2675 2680 2685	
gcc cat cag aaa ctc cgt gaa gat gaa gat gga gca gct cca gct gaa	8112
Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala Ala Pro Ala Glu	
2690 2695 2700	
ata gtt atc cag cct gag cca gtt ccc acc cca gcc ttt cct acg ccc	8160
Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe Pro Thr Pro	
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acc cca gtt ctg aca cat ggt cct tgt gct gca gaa tca gaa cca gct	8208
Thr Pro Val Leu Thr His Gly Pro Cys Ala Ala Glu Ser Glu Pro Ala	
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Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile	

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gca att gca ttt gat gac acc aaa gtt aaa aac cgt ctc aca att gag			8304
Ala Ile Ala Phe Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu			
2755	2760	2765	
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Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Ala			
2770	2775	2780	
gcg atc aat cat gct gat ttt gca aca gtt cag ctg aga aat gga ttg			8400
Ala Ile Asn His Ala Asp Phe Ala Thr Val Gln Leu Arg Asn Gly Leu			
2785	2790	2795	2800
ccc tac ttc agc tat gac ttg ggg agt ggg gac acc cac acc atg atc			8448
Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His Thr Met Ile			
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Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met Arg			
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Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser Asn Arg Thr			
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Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly Met Leu Tyr			
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Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro Val			
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acc tat agc att gat ggc tgc gtc agg aat ctc cac atg gca gag gcc			8688
Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu Ala			
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cct gcc gat ctg gaa caa ccc acc tcc agc ttc cat gtt ggg aca tgt			8736
Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys			
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Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe Asp Gly Thr Gly Phe Ala			
2915	2920	2925	
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Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu Leu Val Glu Phe			
2930	2935	2940	
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Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly Ile Ser Ser			
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caa aaa atg gat gga atg ggt att gaa atg att gat gaa aag ttg atg			8928
Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met			
2965	2970	2975	
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Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Val Tyr Asp Ala			
2980	2985	2990	

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 Gly Val Pro Gly His Leu Cys Asp Gly Gln Trp His Lys Val Thr Ala
 2995 3000 3005
 aac aag atc aaa cac cgc att gag ctc aca gtc gat ggg aac cag gtg 9072
 Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val
 3010 3015 3020
 gaa gcc caa agc cca aac cca gca tct aca tca gct gac aca aat gac 9120
 Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp
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 Pro Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu
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 Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr
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<400> 8
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 Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val
 35 40 45
 Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys
 50 55 60
 Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile Thr Asn Ala
 65 70 75 80
 Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly
 85 90 95
 Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe
 100 105 110
 Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly
 115 120 125

Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp
 130 135 140
 Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile
 145 150 155 160
 Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile
 165 170 175
 Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile
 180 185 190
 His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro
 195 200 205
 Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln
 210 215 220
 Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp
 225 230 235 240
 Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val
 245 250 255
 Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg
 260 265 270
 Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu
 275 280 285
 His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His
 290 295 300
 Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu
 305 310 315 320
 Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn
 325 330 335
 Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly
 340 345 350
 Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys
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 Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn
 370 375 380
 Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu
 385 390 395 400
 Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala
 405 410 415
 Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp
 420 425 430
 Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn
 435 440 445

Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys
 450 455 460
 Ile Cys Lys Glu Asn Val Glu Gly Gly Asp Cys Ser Arg Cys Lys Ser
 465 470 475 480
 Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp Lys Gly Cys Asp Glu Cys
 485 490 495
 Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr
 500 505 510
 Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly
 515 520 525
 Arg Ile Arg Val Ala Pro Gln Gln Asp Asp Leu Asp Ser Pro Gln Gln
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 Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln Ala Leu Pro His Ser Tyr
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 Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly Asn Lys Leu Pro Ala Val
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 Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu
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 Glu Asp Thr Glu Arg Val Leu Gln Leu Met Ile Ile Leu Glu Gly Asn
 595 600 605
 Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu Val Tyr Leu His Pro Ser
 610 615 620
 Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser Phe Thr Ile
 625 630 635 640
 His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met Thr Val Leu
 645 650 655
 Ala Asn Leu Lys Arg Val Leu Leu Gln Ile Thr Tyr Ser Phe Gly Met
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 Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Ala Val Ser
 675 680 685
 Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys
 690 695 700
 Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp Pro Arg His
 705 710 715 720
 Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln
 725 730 735
 Cys Phe Gly His Ala Glu Ser Cys Asp Asp Val Thr Gly Glu Cys Leu
 740 745 750
 Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys Cys Leu Pro
 755 760 765
 Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp Cys Gln Pro

770	775	780
Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys 785 790 795 800		
His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly 805 810 815		
Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln 820 825 830		
Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn 835 840 845		
Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys 850 855 860		
Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala 865 870 875 880		
Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys 885 890 895		
Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr 900 905 910		
Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys 915 920 925		
Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro 930 935 940		
Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Glu Ser 945 950 955 960		
Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg 965 970 975		
Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys 980 985 990		
Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys 995 1000 1005		
Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro 1010 1015 1020		
Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala Cys Asn Cys 1025 1030 1035 1040		
Ser Thr Val Gly Ser Leu Asp Phe Gln Cys Asn Val Asn Thr Gly Gln 1045 1050 1055		
Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr Glu Cys Ser 1060 1065 1070		
Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp Cys Phe Leu 1075 1080 1085		
Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser Glu Thr Lys Lys Cys Ser 1090 1095 1100		

Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys Lys Val Asn Val Glu Gly
 1105 1110 1115 1120
 Ile His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys
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 Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr Thr Thr Gln
 1140 1145 1150
 Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Lys Ala
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 Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr
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 Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu Lys His Leu
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 1730 1735 1740
 Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys

1745	1750	1755	1760
Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Ile Arg	1765	1770	1775
Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu	1780	1785	1790
Glu Lys Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn	1795	1800	1805
Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala	1810	1815	1820
Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys	1825	1830	1835
Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser	1845	1850	1855
Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu	1860	1865	1870
Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile	1875	1880	1885
Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys	1890	1895	1900
Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala	1905	1910	1915
Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly	1925	1930	1935
Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser	1940	1945	1950
Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu	1955	1960	1965
Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu Asn Ala Asp	1970	1975	1980
Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys	1985	1990	1995
Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys	2005	2010	2015
Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln	2020	2025	2030
Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn	2035	2040	2045
Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro	2050	2055	2060
Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val Lys Asn Leu	2065	2070	2075
			2080

Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu
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 Glu Gly Ser Gln Thr Gln Arg Arg Gln Ser Gln Ala His Gln Gln Arg
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 Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile Thr
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acc aat gct aca tgt ggg gaa aaa gga ccc gag atg tac tgc aag ttg 249
 Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu
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 Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile
 70 75 80

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 Cys Asn Gln Asn Ser Ser Asn Pro Tyr Gln Arg His Pro Ile Thr Asn
 85 90 95

gct att gat ggc aag aac aca tgg tgg cag agt ccc agt atc aag aat 393
 Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn
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 Gly Val Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val
 115 120 125

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 Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro
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Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn	
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Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val	
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Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu	
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Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser	
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His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Ser Glu Cys	
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Thr Val Ala Ser Arg Asn Leu Ser Leu Asn Ile His Gly Lys Tyr Ile	
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Cys Glu Thr Cys Val Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro	
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Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Thr Gly Ser	
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Leu Ser Glu Val Cys Val Lys Asp Glu Lys Tyr Ala Gln Arg Gly Leu	
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Lys Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Asn Cys	
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Asp Arg Cys Val Arg Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro Cys	
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Asn Cys Ser Gly Leu Gly Ser Thr Asn Glu Asp Pro Cys Val Gly Pro	
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Cys Ser Cys Lys Glu Asn Val Glu Gly Glu Asp Cys Ser Arg Cys Lys	
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Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Gln Lys Gly Cys Glu Glu	
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Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr	
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Gln Ile Ser Ile Ser Asn Ser Glu Ala Arg Lys Ser Leu Leu Asp Gly	
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Glu Asp Asp Thr Glu Lys Leu Leu Gln Leu Met Ile Ile Phe Glu Gly	
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Ser	Glu	Glu	His	Val	Glu	Glu	Val	Ser	Leu	Lys	Glu	Glu	Ala	Phe	Thr	
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Ile	His	Gly	Thr	Asn	Leu	Pro	Val	Thr	Arg	Lys	Asp	Phe	Met	Ile	Val	
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ctc	aca	aat	ttg	gga	gag	atc	ctt	atc	caa	atc	aca	tac	aac	tta	ggg	2121
Leu	Thr	Asn	Leu	Gly	Glu	Ile	Leu	Ile	Gln	Ile	Thr	Tyr	Asn	Leu	Gly	
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Met	Asp	Ala	Ile	Phe	Arg	Leu	Ser	Ser	Val	Asn	Leu	Glu	Ser	Pro	Val	
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Pro	Tyr	Pro	Thr	Asp	Arg	Arg	Ile	Ala	Thr	Asp	Val	Glu	Val	Cys	Gln	
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Cys	Pro	Pro	Gly	Tyr	Ser	Gly	Ser	Ser	Cys	Glu	Thr	Cys	Trp	Pro	Arg	
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His	Arg	Arg	Val	Asn	Gly	Thr	Ile	Phe	Gly	Gly	Ile	Cys	Glu	Pro	Cys	
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Gln	Cys	Phe	Ala	His	Ala	Glu	Ala	Cys	Asp	Asp	Ile	Thr	Gly	Glu	Cys	
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Leu	Asn	Cys	Lys	Asp	His	Thr	Gly	Gly	Pro	Tyr	Cys	Asn	Glu	Cys	Leu	
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cct	gga	ttc	tat	ggg	gat	cct	act	cga	gga	agc	cct	gaa	gac	tgt	cag	2457
Pro	Gly	Phe	Tyr	Gly	Asp	Pro	Thr	Arg	Gly	Ser	Pro	Glu	Asp	Cys	Gln	
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Pro	Cys	Ala	Cys	Pro	Leu	Asn	Ile	Pro	Ser	Asn	Asn	Phe	Ser	Pro	Thr	
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Cys	His	Leu	Asp	Arg	Ser	Leu	Gly	Leu	Ile	Cys	Asp	Glu	Cys	Pro	Ile	
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Asn	Leu	Asp	Tyr	Ser	Ile	Pro	Gly	Ser	Cys	Asp	Ser	Leu	Ser	Gly	Ser	

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Ala	Asp	Gly	Tyr	Phe	Gly	Asp	Ala	Val	Asn	Thr	Lys	Asn	Cys	Gln	Pro															
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tgc	att	tgc	cca	ccc	aat	acc	act	gga	gaa	aag	tgt	tct	gag	tgt	ctt						3177									
Cys	Ile	Cys	Pro	Pro	Asn	Thr	Thr	Gly	Glu	Lys	Cys	Ser	Glu	Cys	Leu															
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Ser	Arg	Gly	His	Trp	Asn	Tyr	Pro	Leu	Cys	Thr	Leu	Cys	Asp	Cys	Phe															
																1090											1095	1100	1105	
ctt	cca	ggc	aca	gat	gcc	acg	act	tgt	gat	ctg	gag	act	agg	aaa	tgc						3417									
Leu	Pro	Gly	Thr	Asp	Ala	Thr	Thr	Cys	Asp	Leu	Glu	Thr	Arg	Lys	Cys															
																1110											1115	1120		

tcc tgt agt gat caa act gga cag tgc agc tgt aag gtg aat gtg gaa	3465
Ser Cys Ser Asp Gln Thr Gly Gln Cys Ser Cys Lys Val Asn Val Glu	
1125 1130 1135	
ggc gtc cac tgt gac agg tgc cgg cct ggc aaa ttt gga cta gat gcc	3513
Gly Val His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala	
1140 1145 1150	
aag aac cca ctt ggc tgc agc agc tgc tac tgc ttt gga gtt act agt	3561
Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr Ser	
1155 1160 1165	
caa tgc tct gaa gca aag ggg ctg atc cgt acg tgg gtg act ttg agt	3609
Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Ser	
1170 1175 1180 1185	
gat gaa cag acc att cta cct ctg gtg gat gag gcc ctg cag cac acg	3657
Asp Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr	
1190 1195 1200	
act acc aaa ggc att gct ttc cag aaa cca gag att gtt gca aag atg	3705
Thr Thr Lys Gly Ile Ala Phe Gln Lys Pro Glu Ile Val Ala Lys Met	
1205 1210 1215	
gat gaa gtc agg caa gag ctg cat ttg gaa cct ttt tac tgg aaa ctg	3753
Asp Glu Val Arg Gln Glu Leu His Leu Glu Pro Phe Tyr Trp Lys Leu	
1220 1225 1230	
cca caa caa ttt gaa ggg aaa aag ttg atg gct tat ggt ggc aaa ctg	3801
Pro Gln Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu	
1235 1240 1245	
aag tat gcc atc tat ttt gag gct cgg gat gag aca ggc ttt gcc aca	3849
Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala Thr	
1250 1255 1260 1265	
tat aaa cct caa gtt atc att cga ggt gga act cct act cat gct aga	3897
Tyr Lys Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg	
1270 1275 1280	
att att acc aga cac atg gct gcc cct ctg att ggc cag ttg aca cgg	3945
Ile Ile Thr Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg	
1285 1290 1295	
cat gaa ata gaa atg aca gag aaa gaa tgg aaa tat tat ggt gat gat	3993
His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp	
1300 1305 1310	
cct cga atc agt aga act gtg acc cgt gaa gac ttc ttg gat ata cta	4041
Pro Arg Ile Ser Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu	
1315 1320 1325	
tat gat att cac tat atc ctt atc aag gct act tat gga aac gtt gtg	4089
Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val Val	
1330 1335 1340 1345	
aga caa agc cgc att tct gaa atc tcc atg gaa gta gct gaa cca gga	4137
Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Pro Gly	
1350 1355 1360	

cat gta tta gca ggg agc cca cca gca cac ttg ata gaa aga tgc gat	4185
His Val Leu Ala Gly Ser Pro Pro Ala His Leu Ile Glu Arg Cys Asp	
1365 1370 1375	
tgc cct cct ggc tat tct ggc ttg tct tgt gag acg tgt gca cca gga	4233
Cys Pro Pro Gly Tyr Ser Gly Leu Ser Cys Glu Thr Cys Ala Pro Gly	
1380 1385 1390	
ttt tac cga ctt cgt tct gaa cca ggt ggg cgg act cct gga cca acc	4281
Phe Tyr Arg Leu Arg Ser Glu Pro Gly Gly Arg Thr Pro Gly Pro Thr	
1395 1400 1405	
tta ggg acc tgt gtt ccc tgc caa tgt aat gga cac agc agt cag tgt	4329
Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser Gln Cys	
1410 1415 1420 1425	
gat cct gag acc tca gta tgc cag aat tgt cag cat cac act gct ggt	4377
Asp Pro Glu Thr Ser Val Cys Gln Asn Cys Gln His His Thr Ala Gly	
1430 1435 1440	
gac ttc tgt gag cgc tgt gcc ctt ggc tac tat gga atc gtc agg gga	4425
Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val Arg Gly	
1445 1450 1455	
ttg cca aat gac tgc caa cca tgt gct tgt cct ctg att tcg ccc agc	4473
Leu Pro Asn Asp Cys Gln Pro Cys Ala Cys Pro Leu Ile Ser Pro Ser	
1460 1465 1470	
aac aat ttc agc ccc tct tgt gta ttg gaa ggt ctg gaa gat tac cgt	4521
Asn Asn Phe Ser Pro Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr Arg	
1475 1480 1485	
tgc acc gcc tgc cca agg ggc tat gaa gga cag tac tgt gaa agg tgt	4569
Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys	
1490 1495 1500 1505	
gcc cca ggc tat act ggc agc cca agc agc ccc gga ggc tcc tgc caa	4617
Ala Pro Gly Tyr Thr Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys Gln	
1510 1515 1520	
gaa tgt gag tgt gac cct tat ggc tcc cta ccg gtt ccc tgt gac cgg	4665
Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Arg	
1525 1530 1535	
gtc aca gga ctc tgc acg tgc cgc cct gga gcc aca gga agg aag tgt	4713
Val Thr Gly Leu Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys	
1540 1545 1550	
gat ggc tgc gag cac tgg cat gca cgc gag ggt gca gag tgt gtc ttt	4761
Asp Gly Cys Glu His Trp His Ala Arg Glu Gly Ala Glu Cys Val Phe	
1555 1560 1565	
tgt gga gac gag tgt aca ggc ctt ctt ctt ggt gac ctg gct cgt cta	4809
Cys Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala Arg Leu	
1570 1575 1580 1585	
gag cag atg acc atg aac atc aac ctc acg ggc cca ctg cct gct cca	4857
Glu Gln Met Thr Met Asn Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro	
1590 1595 1600	
tat aaa att ctg tat ggt ctt gaa aat aca act cag gaa ctc aag cac	4905

Tyr	Lys	Ile	Leu	Tyr	Gly	Leu	Glu	Asn	Thr	Thr	Gln	Glu	Leu	Lys	His	
			1605					1610					1615			
ctg	cta	tca	ccg	caa	cgg	gca	cca	gag	agg	ctc	att	cag	ttg	gca	gag	4953
Leu	Leu	Ser	Pro	Gln	Arg	Ala	Pro	Glu	Arg	Leu	Ile	Gln	Leu	Ala	Glu	
			1620				1625				1630					
ggc	aac	gtg	aac	aca	ctt	gtg	atg	gaa	aca	aat	gag	ctg	cta	acc	aga	5001
Gly	Asn	Val	Asn	Thr	Leu	Val	Met	Glu	Thr	Asn	Glu	Leu	Leu	Thr	Arg	
			1635			1640				1645						
gca	acc	aaa	gtg	aca	gca	gat	ggg	gag	caa	aca	gga	caa	gat	gct	gag	5049
Ala	Thr	Lys	Val	Thr	Ala	Asp	Gly	Glu	Gln	Thr	Gly	Gln	Asp	Ala	Glu	
1650					1655					1660				1665		
agg	acc	aac	tcc	aga	gca	gaa	tcc	ttg	gaa	gaa	ttc	att	aaa	ggg	ctt	5097
Arg	Thr	Asn	Ser	Arg	Ala	Glu	Ser	Leu	Glu	Glu	Phe	Ile	Lys	Gly	Leu	
			1670					1675					1680			
gtc	cag	gat	gct	gaa	gcc	ata	aat	gaa	aaa	gct	gta	aaa	cta	aat	gaa	5145
Val	Gln	Asp	Ala	Glu	Ala	Ile	Asn	Glu	Lys	Ala	Val	Lys	Leu	Asn	Glu	
			1685				1690					1695				
acc	tta	gga	aat	caa	gat	aag	aca	gca	gag	aga	aac	ttg	gag	gag	ctt	5193
Thr	Leu	Gly	Asn	Gln	Asp	Lys	Thr	Ala	Glu	Arg	Asn	Leu	Glu	Glu	Leu	
			1700			1705					1710					
caa	aag	gaa	atc	gac	cgg	atg	ctg	aag	gaa	ctg	aga	agt	aaa	gat	ctt	5241
Gln	Lys	Glu	Ile	Asp	Arg	Met	Leu	Lys	Glu	Leu	Arg	Ser	Lys	Asp	Leu	
			1715			1720				1725						
caa	aca	cag	aag	gaa	gtt	gct	gag	gat	gag	ctc	gtg	gca	gca	gaa	ggc	5289
Gln	Thr	Gln	Lys	Glu	Val	Ala	Glu	Asp	Glu	Leu	Val	Ala	Ala	Glu	Gly	
1730				1735					1740					1745		
ctt	ctg	aag	aga	gta	aac	aag	ctg	ttt	gga	gag	ccc	aga	gcc	cag	aat	5337
Leu	Leu	Lys	Arg	Val	Asn	Lys	Leu	Phe	Gly	Glu	Pro	Arg	Ala	Gln	Asn	
			1750				1755					1760				
gaa	gat	atg	gaa	aag	gat	ctc	cag	cag	aaa	ctg	gca	gag	tac	aag	aac	5385
Glu	Asp	Met	Glu	Lys	Asp	Leu	Gln	Gln	Lys	Leu	Ala	Glu	Tyr	Lys	Asn	
			1765			1770					1775					
aaa	ctt	gat	gat	gct	tgg	gat	cta	ttg	aga	gaa	gcc	act	gat	aaa	acc	5433
Lys	Leu	Asp	Asp	Ala	Trp	Asp	Leu	Leu	Arg	Glu	Ala	Thr	Asp	Lys	Thr	
			1780			1785					1790					
cga	gat	gct	aat	cgt	ttg	tct	gct	gcc	aat	caa	aaa	aac	atg	acc	ata	5481
Arg	Asp	Ala	Asn	Arg	Leu	Ser	Ala	Ala	Asn	Gln	Lys	Asn	Met	Thr	Ile	
			1795		1800					1805						
ctg	gag	aca	aag	aag	gag	gct	att	gaa	ggg	agc	aaa	cga	caa	ata	gag	5529
Leu	Glu	Thr	Lys	Lys	Glu	Ala	Ile	Glu	Gly	Ser	Lys	Arg	Gln	Ile	Glu	
1810				1815				1820					1825			
aac	act	tta	aag	gaa	ggc	aat	gac	atc	ctt	gat	gaa	gcc	aat	caa	ctc	5577
Asn	Thr	Leu	Lys	Glu	Gly	Asn	Asp	Ile	Leu	Asp	Glu	Ala	Asn	Gln	Leu	
			1830			1835					1840					
tta	ggg	gaa	atc	aac	tca	gtc	ata	gat	tat	gtc	gac	gac	att	aaa	act	5625
Leu	Gly	Glu	Ile	Asn	Ser	Val	Ile	Asp	Tyr	Val	Asp	Asp	Ile	Lys	Thr	

1845	1850	1855	
aag ttg cca cca atg tcc gag gag ctg agt gac aaa ata gat gac ctc			5673
Lys Leu Pro Pro Met Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp Leu			
1860	1865	1870	
gcc cag gaa ata aag gac aga agg ctt gct gag aag gtg ttc cag gct			5721
Ala Gln Glu Ile Lys Asp Arg Arg Leu Ala Glu Lys Val Phe Gln Ala			
1875	1880	1885	
gag agc cat gct gct cag ctg aac gac tcg tct gct gta ctt gat gga			5769
Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly			
1890	1895	1900	1905
atc ctg gat gag gct aag aac atc tct ttc aat gcc acg gca gcc ttc			5817
Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe			
1910	1915	1920	
aga gct tac agt aat att aaa gac tac att gat gaa gct gag aaa gtg			5865
Arg Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val			
1925	1930	1935	
gcc aga gaa gcc aaa gag ctt gcc caa ggg gct aca aaa ctg gca aca			5913
Ala Arg Glu Ala Lys Glu Leu Ala Gln Gly Ala Thr Lys Leu Ala Thr			
1940	1945	1950	
agt cct cag ggc tta tta aaa gaa gat gcc aaa ggc tcc ctt cag aaa			5961
Ser Pro Gln Gly Leu Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln Lys			
1955	1960	1965	
agc ttc agg atc ctc aat gaa gcc aag aag cta gca aac gat gtg aaa			6009
Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys			
1970	1975	1980	1985
gga aat cac aat gat cta aat gac ctg aaa acc agg tta gaa act gct			6057
Gly Asn His Asn Asp Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr Ala			
1990	1995	2000	
gac ctt aga aac agt gga ctt cta gga gct cta aat gac acc atg gac			6105
Asp Leu Arg Asn Ser Gly Leu Leu Gly Ala Leu Asn Asp Thr Met Asp			
2005	2010	2015	
aag tta tca gcc att aca aat gac acg gct gct aaa ctg cag gct gtc			6153
Lys Leu Ser Ala Ile Thr Asn Asp Thr Ala Ala Lys Leu Gln Ala Val			
2020	2025	2030	
aaa gag aaa gcc aga gaa gcc aat gac aca gca aaa gct gtc ctg gcc			6201
Lys Glu Lys Ala Arg Glu Ala Asn Asp Thr Ala Lys Ala Val Leu Ala			
2035	2040	2045	
cag gtt aag gac ctg cat cag aac cta gat ggc ctg aag caa aac tac			6249
Gln Val Lys Asp Leu His Gln Asn Leu Asp Gly Leu Lys Gln Asn Tyr			
2050	2055	2060	2065
aat aaa ctg gca gac agc gtg gcc aaa acg aac gct gtg gtg aaa gat			6297
Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp			
2070	2075	2080	
cct tcc aaa aac aaa atc att gca gat gca ggc act tcc gtg aga aat			6345
Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Gly Thr Ser Val Arg Asn			
2085	2090	2095	

cta gaa cag gaa gct gac cgg cta atc gac aaa ctc aag ccc atc aag Leu Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys 2100 2105 2110	6393
gag ctt gag gac aac cta aag aaa aac att tct gaa ata aag gaa ctg Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu 2115 2120 2125	6441
atc aac caa gct cgg aaa caa gct aac tct atc aaa gta tct gtt tct Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser 2130 2135 2140 2145	6489
tcg gga ggt gac tgt gtt cgg aca tac agg cca gaa atc aag aaa gga Ser Gly Gly Asp Cys Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys Gly 2150 2155 2160	6537
agc tac aat aac atc gtt gtc cat gtc aag acc gct gtt gcc gac aac Ser Tyr Asn Asn Ile Val Val His Val Lys Thr Ala Val Ala Asp Asn 2165 2170 2175	6585
ctc ctt ttt tat ctt gga agt gcc aaa ttt att gac ttt ctt gct ata Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile 2180 2185 2190	6633
gaa atg cgc aaa ggc aaa gtc agc ttc ctc tgg att gtt ggc tct gga Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp Ile Val Gly Ser Gly 2195 2200 2205	6681
gtt ggc cga gta ggg ttt cca gac ttg acc atc gac gac tcc tat tgg Val Gly Arg Val Gly Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp 2210 2215 2220 2225	6729
tac cgt att gaa gca tca aga acg gga aga aat gga tct att tct gtg Tyr Arg Ile Glu Ala Ser Arg Thr Gly Arg Asn Gly Ser Ile Ser Val 2230 2235 2240	6777
aga gct tta gat gga ccc aaa gcc agt atg gta ccc agc acc tac cat Arg Ala Leu Asp Gly Pro Lys Ala Ser Met Val Pro Ser Thr Tyr His 2245 2250 2255	6825
tca gtg tct cct ccc ggg tat act atc cta gat gtg gat gca aat gca Ser Val Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala 2260 2265 2270	6873
atg ctg ttt gtt ggt ggc ctg acc gga aaa ata aag aag gcc gat gct Met Leu Phe Val Gly Gly Leu Thr Gly Lys Ile Lys Lys Ala Asp Ala 2275 2280 2285	6921
gta cgt gtg atc acc ttc acc ggc tgt atg gga gaa aca tac ttt gac Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp 2290 2295 2300 2305	6969
aac aaa cct ata ggt tta tgg aac ttc cgg gag aaa gaa ggc gac tgt Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys 2310 2315 2320	7017
aag gga tgt act gtc agc cca caa gtg gaa gat agt gag ggg act att Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile 2325 2330 2335	7065

cag ttt gat ggt gaa ggc tat gca tta gtg agc cgg ccc atc cgc tgg Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp 2340 2345 2350	7113
tac ccc aac atc tcc aca gtc atg ttc aag ttc cgg aca ttt tca tca Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser 2355 2360 2365	7161
agt gct ctc ctg atg tat ctt gcc aca cga gac ctg aaa gat ttc atg Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe Met 2370 2375 2380 2385	7209
agt gta gag ctc agt gat gga cat gtg aaa gtc agc tat gac ctg ggc Ser Val Glu Leu Ser Asp Gly His Val Lys Val Ser Tyr Asp Leu Gly 2390 2395 2400	7257
tca gga atg act tcc gtt gtc agc aat caa aac cat aat gat ggg aaa Ser Gly Met Thr Ser Val Val Ser Asn Gln Asn His Asn Asp Gly Lys 2405 2410 2415	7305
tgg aaa gca ttc acg ctg tgc cgg att cag aaa caa gcc aac ata tgc Trp Lys Ala Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser 2420 2425 2430	7353
att gtc gac atc gat tct aac cag gag gag aat gta gct act tca tct Ile Val Asp Ile Asp Ser Asn Gln Glu Glu Asn Val Ala Thr Ser Ser 2435 2440 2445	7401
tct gga aac aac ttt ggt ctt gac ttg aaa gca gat gac aaa ata tat Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr 2450 2455 2460 2465	7449
ttt ggt ggc ctg cca act ctg aga aac ttg agt atg aaa gca agg cca Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro 2470 2475 2480	7497
gaa gtc aat gtg aag aaa tac tcc ggc tgc ctc aaa gat att gaa att Glu Val Asn Val Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile 2485 2490 2495	7545
tca aga aca cct tac aat ata ctc agc agc cct gat tat gtt ggt gtg Ser Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val 2500 2505 2510	7593
acc aaa ggc tgt tca ctg gag aat gtt aat aca gtt agt ttc ccc aag Thr Lys Gly Cys Ser Leu Glu Asn Val Asn Thr Val Ser Phe Pro Lys 2515 2520 2525	7641
cct ggt ttt gtg gag ctt gcc gct gtg tct att gat gtt gga aca gaa Pro Gly Phe Val Glu Leu Ala Ala Val Ser Ile Asp Val Gly Thr Glu 2530 2535 2540 2545	7689
atc aat ctg tcc ttt agt acc agg aac gag tct ggg atc att ctc ttg Ile Asn Leu Ser Phe Ser Thr Arg Asn Glu Ser Gly Ile Ile Leu Leu 2550 2555 2560	7737
gga agt gga ggg aca ctc aca cca ccc agg aga aaa cgg aga caa acc Gly Ser Gly Gly Thr Leu Thr Pro Pro Arg Arg Lys Arg Arg Gln Thr 2565 2570 2575	7785
aca cag gct tat tat gcc ata ttc ctc aac aag ggc cgc ttg gaa gtg	7833

Thr Gln Ala Tyr Tyr Ala Ile Phe Leu Asn Lys Gly Arg Leu Glu Val	
2580 2585 2590	
cat ctc tcc tcg ggg aca cgg aca atg agg aaa att gtc atc aaa ccg	7881
His Leu Ser Ser Gly Thr Arg Thr Met Arg Lys Ile Val Ile Lys Pro	
2595 2600 2605	
gag cca aat ttg ttt cat gat ggg aga gaa cat tct gtc cac gta gaa	7929
Glu Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val Glu	
2610 2615 2620 2625	
aga acc aga ggc atc ttc act gtt caa att gat gaa gac aga aga cat	7977
Arg Thr Arg Gly Ile Phe Thr Val Gln Ile Asp Glu Asp Arg Arg His	
2630 2635 2640	
atc caa aac ctg aca gag gaa cag ccc atc gaa gtg aaa aag ctc ttt	8025
Ile Gln Asn Leu Thr Glu Glu Gln Pro Ile Glu Val Lys Lys Leu Phe	
2645 2650 2655	
gtc ggg ggt gct cct cct gaa ttt cag ccc tcc cca ctc agg aat att	8073
Val Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile	
2660 2665 2670	
ccg gcc ttt caa ggc tgt gtg tgg aac ctt gtt att aac tcc atc ccc	8121
Pro Ala Phe Gln Gly Cys Val Trp Asn Leu Val Ile Asn Ser Ile Pro	
2675 2680 2685	
atg gac ttt gcg cag cct ata gcc ttc aaa aat gcc gac att ggt cgc	8169
Met Asp Phe Ala Gln Pro Ile Ala Phe Lys Asn Ala Asp Ile Gly Arg	
2690 2695 2700 2705	
tgt acc tat caa aag ccc cgg gaa gat gag agt gaa gca gtt cca gct	8217
Cys Thr Tyr Gln Lys Pro Arg Glu Asp Glu Ser Glu Ala Val Pro Ala	
2710 2715 2720	
gaa gtt att gtc cag cct cag tcg gtg ccc acc cct gcc ttc cct ttc	8265
Glu Val Ile Val Gln Pro Gln Ser Val Pro Thr Pro Ala Phe Pro Phe	
2725 2730 2735	
cca gtc ccc acc atg gtg cat ggc cct tgt gtt gca gaa tca gaa cca	8313
Pro Val Pro Thr Met Val His Gly Pro Cys Val Ala Glu Ser Glu Pro	
2740 2745 2750	
gct ctt ctg aca ggg agc aag cag ttt ggg ctt tcc aga aac agc cac	8361
Ala Leu Leu Thr Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His	
2755 2760 2765	
att gca att gtc ttt gat gac acc aaa gtt aaa aac cgc ctc acc att	8409
Ile Ala Ile Val Phe Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile	
2770 2775 2780 2785	
gag ctg gag gta cga act gaa gct gaa tca ggc ttg ctc ttc tac atg	8457
Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met	
2790 2795 2800	
ggt cgg atc aat cat gct gat ttt ggt act gtt cag ctg agg aat ggg	8505
Gly Arg Ile Asn His Ala Asp Phe Gly Thr Val Gln Leu Arg Asn Gly	
2805 2810 2815	
ttc ccg ttc ttc agt tat gat ttg ggg agt ggg agc acc aga acc atg	8553
Phe Pro Phe Phe Ser Tyr Asp Leu Gly Ser Gly Ser Thr Arg Thr Met	

2820	2825	2830	
atc ccc aca aaa atc aac gat ggt cag tgg cac aag att aag att gtg Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Val 2835 2840 2845			8601
aga gtg aag cag gag gga att ctt tat gtg gat gat gcc tcc agc caa Arg Val Lys Gln Glu Gly Ile Leu Tyr Val Asp Asp Ala Ser Ser Gln 2850 2855 2860 2865			8649
acc atc agt ccc aag aaa gcc gac atc ctg gat gtc ggg ggg att ctg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Gly Gly Ile Leu 2870 2875 2880			8697
tat gtc ggt gga ttg ccg atc aac tat acc aca cgc aga att ggt cca Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro 2885 2890 2895			8745
gtg act tac agc ctg gat ggc tgt gtt agg aat ctt cac atg gaa caa Val Thr Tyr Ser Leu Asp Gly Cys Val Arg Asn Leu His Met. Glu Gln 2900 2905 2910			8793
gcc cct gtt gat ctg gac cag cct acc tcc agc ttt cac gtt ggg aca Ala Pro Val Asp Leu Asp Gln Pro Thr Ser Ser Phe His Val Gly Thr 2915 2920 2925			8841
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Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp	1890	1895	1900
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Phe Arg Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys	1925	1930	1935
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Thr Ser Pro Gln Gly Leu Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln	1955	1960	1965
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Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr	
210 215 220	
ttg aat gca gac ttg atg atg ttt gct cac aaa gac ccc aga gaa atc	720
Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp Pro Arg Glu Ile	
225 230 235 240	
gat ccc att gtc aca cga aga tat tac tat tct gtc aag gat att tca	768
Asp Pro Ile Val Thr Arg Arg Tyr Tyr Ser Val Lys Asp Ile Ser	
245 250 255	
gtt ggc ggg atg tgc atc tgt tat ggt cat gcc cgg gct tgt cca ctt	816
Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg Ala Cys Pro Leu	
260 265 270	
gac cct gca aca aat aaa tca cgc tgt gag tgt gaa cat aac acc tgt	864
Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys	
275 280 285	
ggg gaa agc tgt gac agg tgc tgt cca gga ttc cat cag aag cct tgg	912
Gly Glu Ser Cys Asp Arg Cys Cys Pro Gly Phe His Gln Lys Pro Trp	
290 295 300	
aga gct gga acc ttc ctc acc aag tct gag tgt gaa gca tgc aat tgt	960
Arg Ala Gly Thr Phe Leu Thr Lys Ser Glu Cys Glu Ala Cys Asn Cys	
305 310 315 320	
cac gga aaa gct gag gaa tgc tat tat gat gaa act gtt gct agc aga	1008
His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Thr Val Ala Ser Arg	
325 330 335	
aat cta agt tta aat ata cat ggg aag tac atc gga ggg ggt gtg tgc	1056
Asn Leu Ser Leu Asn Ile His Gly Lys Tyr Ile Gly Gly Val Cys	
340 345 350	
atc aac tgc aca cat aac acg gct ggg ata aat tgt gag aca tgt gtt	1104
Ile Asn Cys Thr His Asn Thr Ala Gly Ile Asn Cys Glu Thr Cys Val	
355 360 365	
gat gga ttc ttc aga ccc aaa ggg gtg tca cca aat tat cca aga cca	1152
Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro	
370 375 380	
tgc cag cca tgt cac tgt gat cca act ggc tcc ctt agt gaa gtc tgt	1200
Cys Gln Pro Cys His Cys Asp Pro Thr Gly Ser Leu Ser Glu Val Cys	
385 390 395 400	
gtc aaa gat gag aaa tac gcc cag cga ggg ttg aaa cct gga tcc tgt	1248
Val Lys Asp Glu Lys Tyr Ala Gln Arg Gly Leu Lys Pro Gly Ser Cys	
405 410 415	
cac tgc aaa act ggc ttt gga ggc gtg aac tgt gat cgc tgt gtc agg	1296
His Cys Lys Thr Gly Phe Gly Gly Val Asn Cys Asp Arg Cys Val Arg	
420 425 430	
ggg tac cat ggt tac cca gac tgc caa ccc tgt aac tgt agt ggc ttg	1344
Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro Cys Asn Cys Ser Gly Leu	
435 440 445	
ggg agc aca aat gag gac cct tgc gtt ggg ccc tgt agc tgt aag gag	1392

Gly	Ser	Thr	Asn	Glu	Asp	Pro	Cys	Val	Gly	Pro	Cys	Ser	Cys	Lys	Glu	
450						455				460						
aat	ggt	gaa	ggt	gaa	gac	tgt	agt	cgt	tgc	aaa	tct	ggt	ttc	ttc	aac	1440
Asn	Val	Glu	Gly	Glu	Asp	Cys	Ser	Arg	Cys	Lys	Ser	Gly	Phe	Phe	Asn	
465					470					475					480	
ttg	caa	gaa	gat	aat	cag	aaa	ggc	tgt	gag	gag	tgt	ttc	tgt	tca	gga	1488
Leu	Gln	Glu	Asp	Asn	Gln	Lys	Gly	Cys	Glu	Glu	Cys	Phe	Cys	Ser	Gly	
				485					490					495		
gta	tca	aac	aga	tgt	cag	agt	tcc	tac	tgg	acc	tat	ggg	aat	att	caa	1536
Val	Ser	Asn	Arg	Cys	Gln	Ser	Ser	Tyr	Trp	Thr	Tyr	Gly	Asn	Ile	Gln	
			500					505					510			
gac	atg	cgt	ggt	tgg	tat	ctc	aca	gac	ctc	tct	ggc	cgc	att	cgg	atg	1584
Asp	Met	Arg	Gly	Trp	Tyr	Leu	Thr	Asp	Leu	Ser	Gly	Arg	Ile	Arg	Met	
		515					520					525				
gct	ccc	cag	ctt	gat	aac	cct	gac	tca	cct	cag	cag	atc	agc	atc	agt	1632
Ala	Pro	Gln	Leu	Asp	Asn	Pro	Asp	Ser	Pro	Gln	Gln	Ile	Ser	Ile	Ser	
			530			535						540				
aac	tct	gag	gcc	cgg	aaa	tcc	ctg	ctt	gat	ggg	tac	tac	tgg	agt	gca	1680
Asn	Ser	Glu	Ala	Arg	Lys	Ser	Leu	Leu	Asp	Gly	Tyr	Tyr	Trp	Ser	Ala	
545					550					555					560	
cgg	cct	cca	tat	ctg	gga	aac	aga	ctt	cca	gct	gtt	ggg	gga	cag	ttg	1728
Pro	Pro	Pro	Tyr	Leu	Gly	Asn	Arg	Leu	Pro	Ala	Val	Gly	Gly	Gln	Leu	
				565					570					575		
tca	ttt	acc	atc	tca	tat	gac	ctc	gaa	gaa	gag	gaa	gac	gat	aca	gaa	1776
Ser	Phe	Thr	Ile	Ser	Tyr	Asp	Leu	Glu	Glu	Glu	Glu	Asp	Asp	Thr	Glu	
			580					585					590			
aaa	ctc	ctt	cag	ctg	atg	att	atc	ttt	gag	gga	aat	gac	tta	aga	atc	1824
Lys	Leu	Gln	Gln	Leu	Met	Ile	Ile	Phe	Glu	Gly	Asn	Asp	Leu	Arg	Ile	
		595				600						605				
agc	aca	gcg	tat	aag	gag	gtg	tac	tta	gag	cca	tct	gaa	gaa	cac	gtt	1872
Ser	Thr	Ala	Tyr	Lys	Glu	Val	Tyr	Leu	Glu	Pro	Ser	Glu	Glu	His	Val	
		610				615						620				
gag	gag	gtg	tca	ctc	aaa	gaa	gag	gcc	ttt	act	ata	cat	gga	aca	aat	1920
Glu	Glu	Val	Ser	Leu	Lys	Glu	Glu	Ala	Phe	Thr	Ile	His	Gly	Thr	Asn	
625					630					635					640	
ttg	cca	gtc	act	aga	aaa	gat	ttc	atg	att	gtt	ctc	aca	aat	ttg	gga	1968
Leu	Pro	Val	Thr	Arg	Lys	Asp	Phe	Met	Ile	Val	Leu	Thr	Asn	Leu	Gly	
				645					650					655		
gag	atc	ctt	atc	caa	atc	aca	tac	aac	tta	ggg	atg	gac	gcc	atc	ttc	2016
Glu	Ile	Leu	Ile	Gln	Ile	Thr	Tyr	Asn	Leu	Gly	Met	Asp	Ala	Ile	Phe	
			660					665					670			
agg	ctg	agt	tct	gtc	aat	ctt	gaa	tct	cct	gtc	cct	tat	cct	act	gat	2064
Arg	Leu	Ser	Ser	Val	Asn	Leu	Glu	Ser	Pro	Val	Pro	Tyr	Pro	Thr	Asp	
		675				680						685				
aga	cgt	att	gca	act	gat	gtg	gaa	gtt	tgc	cag	tgt	cca	cct	ggg	tac	2112
Arg	Arg	Ile	Ala	Thr	Asp	Val	Glu	Val	Cys	Gln	Cys	Pro	Pro	Gly	Tyr	

690	695	700	
agt ggc agc tct tgt gaa aca tgt tgg cct agg cac cga aga gtt aac			2160
Ser Gly Ser Ser Cys Glu Thr Cys Trp Pro Arg His Arg Arg Val Asn			
705	710	715	720
ggc acc att ttt ggt ggc att tgt gaa cca tgt cag tgc ttt gct cat			2208
Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln Cys Phe Ala His			
	725	730	735
gca gaa gcc tgt gat gac atc aca gga gaa tgt ctg aac tgt aag gat			2256
Ala Glu Ala Cys Asp Asp Ile Thr Gly Glu Cys Leu Asn Cys Lys Asp			
	740	745	750
cac aca ggt ggg ccg tac tgc aat gaa tgt ctc cct gga ttc tat ggt			2304
His Thr Gly Gly Pro Tyr Cys Asn Glu Cys Leu Pro Gly Phe Tyr Gly			
	755	760	765
gat cct act cga gga agc cct gaa gac tgt cag ccc tgt gcc tgt cca			2352
Asp Pro Thr Arg Gly Ser Pro Glu Asp Cys Gln Pro Cys Ala Cys Pro			
	770	775	780
ctc aat atc cca tca aat aac ttt agt cca aca tgc cat tta gac cgg			2400
Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys His Leu Asp Arg			
	785	790	800
agt ctg gga ttg atc tgt gac gag tgt cct att ggg tac aca gga ccg			2448
Ser Leu Gly Leu Ile Cys Asp Glu Cys Pro Ile Gly Tyr Thr Gly Pro			
	805	810	815
cgc tgt gag agg tgt gca gaa ggc tat ttt gga caa cct tcc gta cct			2496
Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro			
	820	825	830
gga gga tca tgt cag cca tgc caa tgc aat gac aac ctt gac tac tcc			2544
Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn Leu Asp Tyr Ser			
	835	840	845
atc cct ggc agc tgt gac agc ctg tct ggc tcc tgt ctg att tgt aag			2592
Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys			
	850	855	860
cca ggt aca aca ggc cgg tac tgt gag ctc tgt gct gat ggg tat ttt			2640
Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe			
	865	870	875
gga gac gcg gtt aat aca aag aac tgt caa cca tgc cgt tgt gat atc			2688
Gly Asp Ala Val Asn Thr Lys Asn Cys Gln Pro Cys Arg Cys Asp Ile			
	885	890	895
aat ggc tcc ttc tca gag gat tgt cac aca aga act ggg caa tgt gag			2736
Asn Gly Ser Phe Ser Glu Asp Cys His Thr Arg Thr Gly Gln Cys Glu			
	900	905	910
tgc aga ccc aat gtt cag ggg cgg cac tgt gac gag tgt aag cct gaa			2784
Cys Arg Pro Asn Val Gln Gly Arg His Cys Asp Glu Cys Lys Pro Glu			
	915	920	925
acc ttt ggc ctg caa ctg gga agg ggt tgt ctg ccc tgc aac tgc aat			2832
Thr Phe Gly Leu Gln Leu Gly Arg Gly Cys Leu Pro Cys Asn Cys Asn			
	930	935	940

tct ttt ggg tct aag tcc ttt gac tgt gaa gca agt ggg cag tgc tgg	2880
Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Ala Ser Gly Gln Cys Trp	
945 950 955 960	
tgc cag cct gga gta gca ggg aag aaa tgt gac cgt tgt gcc cat ggc	2928
Cys Gln Pro Gly Val Ala Gly Lys Lys Cys Asp Arg Cys Ala His Gly	
965 970 975	
tac ttc aac ttc caa gaa gga ggc tgc ata gct tgt gac tgt tct cat	2976
Tyr Phe Asn Phe Gln Glu Gly Cys Ile Ala Cys Asp Cys Ser His	
980 985 990	
ctg ggc aac aac tgt gac cca aaa act ggc caa tgc att tgc cca ccc	3024
Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Gln Cys Ile Cys Pro Pro	
995 1000 1005	
aat acc act gga gaa aag tgt tct gag tgt ctt ccc aac acc tgg ggt	3072
Asn Thr Thr Gly Glu Lys Cys Ser Glu Cys Leu Pro Asn Thr Trp Gly	
1010 1015 1020	
cac agc att gtc acc ggc tgt aag gtt tgt aac tgc agc act gtg ggg	3120
His Ser Ile Val Thr Gly Cys Lys Val Cys Asn Cys Ser Thr Val Gly	
1025 1030 1035 1040	
tcc ttg gct tct cag tgc aat gta aac acg ggc cag tgc agc tgt cat	3168
Ser Leu Ala Ser Gln Cys Asn Val Asn Thr Gly Gln Cys Ser Cys His	
1045 1050 1055	
cca aaa ttc tct ggt atg aaa tgc tca gag tgc agc cga ggt cac tgg	3216
Pro Lys Phe Ser Gly Met Lys Cys Ser Glu Cys Ser Arg Gly His Trp	
1060 1065 1070	
aac tat cct ctc tgc act cta tgt gac tgc ttc ctt cca ggc aca gat	3264
Asn Tyr Pro Leu Cys Thr Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp	
1075 1080 1085	
gcc acg act tgt gat ctg gag act agg aaa tgc tcc tgt agt gat caa	3312
Ala Thr Thr Cys Asp Leu Glu Thr Arg Lys Cys Ser Cys Ser Asp Gln	
1090 1095 1100	
act gga cag tgc agc tgt aag gtg aat gtg gaa ggc gtc cac tgt gac	3360
Thr Gly Gln Cys Ser Cys Lys Val Asn Val Glu Gly Val His Cys Asp	
1105 1110 1115 1120	
agg tgc cgg cct ggc aaa ttt gga cta gat gcc aag aac cca ctt ggc	3408
Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys Asn Pro Leu Gly	
1125 1130 1135	
tgc agc agc tgc tac tgc ttt gga gtt act agt caa tgc tct gaa gca	3456
Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr Ser Gln Cys Ser Glu Ala	
1140 1145 1150	
aag ggg ctg atc cgt acg tgg gtg act ttg agt gat gaa cag acc att	3504
Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Ser Asp Glu Gln Thr Ile	
1155 1160 1165	
cta cct ctg gtg gat gag gcc ctg cag cac acg act acc aaa ggc att	3552
Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr Thr Lys Gly Ile	
1170 1175 1180	

gct ttc cag aaa cca gag att gtt gca aag atg gat gaa gtc agg caa	3600
Ala Phe Gln Lys Pro Glu Ile Val Ala Lys Met Asp Glu Val Arg Gln	
1185 1190 1195 1200	
gag ctc cat ttg gaa cct ttt tac tgg aaa ctc cca caa caa ttt gaa	3648
Glu Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro Gln Gln Phe Glu	
1205 1210 1215	
ggg aaa aag ttg atg gct tat ggt ggc aaa ctc aag tat gcc atc tat	3696
Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr	
1220 1225 1230	
ttt gag gct cgg gat gag aca ggc ttt gcc aca tat aaa cct caa gtt	3744
Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala Thr Tyr Lys Pro Gln Val	
1235 1240 1245	
atc att cga ggt gga act cct act cat gct aga att att acc aga cac	3792
Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile Ile Thr Arg His	
1250 1255 1260	
atg gct gcc cct ctc att ggc cag ttg aca cgg cat gaa ata gaa atg	3840
Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His Glu Ile Glu Met	
1265 1270 1275 1280	
aca gag aaa gaa tgg aaa tat tat ggt gat gat cct cga atc agt aga	3888
Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro Arg Ile Ser Arg	
1285 1290 1295	
act gtg acc cgt gaa gac ttc ttg gat ata cta tat gat att cac tat	3936
Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr Asp Ile His Tyr	
1300 1305 1310	
atc ctt atc aag gct act tat gga aac gtt gtg aga caa agc cgc att	3984
Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val Val Arg Gln Ser Arg Ile	
1315 1320 1325	
tct gaa atc tcc atg gaa gta gct gaa cca gga cat gta tta gca ggg	4032
Ser Glu Ile Ser Met Glu Val Ala Glu Pro Gly His Val Leu Ala Gly	
1330 1335 1340	
agc cca cca gca cac ttg ata gaa aga tgc gat tgc cct cct ggc tat	4080
Ser Pro Pro Ala His Leu Ile Glu Arg Cys Asp Cys Pro Pro Gly Tyr	
1345 1350 1355 1360	
tct ggc ttg tct tgt gag acg tgt gca cca gga ttt tac cga ctt cgt	4128
Ser Gly Leu Ser Cys Glu Thr Cys Ala Pro Gly Phe Tyr Arg Leu Arg	
1365 1370 1375	
tct gaa cca ggt ggg cgg act cct gga cca acc tta ggg acc tgt gtt	4176
Ser Glu Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu Gly Thr Cys Val	
1380 1385 1390	
ccc tgc caa tgt aat gga cac agc agt cag tgt gat cct gag acc tca	4224
Pro Cys Gln Cys Asn Gly His Ser Ser Gln Cys Asp Pro Glu Thr Ser	
1395 1400 1405	
gta tgc cag aat tgt cag cat cac act gct ggt gac ttc tgt gag cgc	4272
Val Cys Gln Asn Cys Gln His His Thr Ala Gly Asp Phe Cys Glu Arg	
1410 1415 1420	
tgt gcc ctt ggc tac tat gga atc gtc agg gga ttg cca aat gac tgc	4320

Cys Ala Leu Gly Tyr Tyr Gly Ile Val Arg Gly Leu Pro Asn Asp Cys	1425	1430	1435	1440	
caa cca tgt gct tgt cct ctg att tcg ccc agc aac aat ttc agc ccc	Gln Pro Cys Ala Cys Pro Leu Ile Ser Pro Ser Asn Asn Phe Ser Pro	1445	1450	1455	4368
tct tgt gta ttg gaa ggt ctg gaa gat tac cgt tgc acc gcc tgc cca	Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr Arg Cys Thr Ala Cys Pro	1460	1465	1470	4416
agg ggc tat gaa gga cag tac tgt gaa agg tgt gcc cca ggc tat act	Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr	1475	1480	1485	4464
ggc agc cca agc agc ccc gga ggc tcc tgc caa gaa tgt gag tgt gac	Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys Gln Glu Cys Glu Cys Asp	1490	1495	1500	4512
cct tat ggc tcc cta ccg gtt ccc tgt gac cgg gtc aca gga ctc tgc	Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Arg Val Thr Gly Leu Cys	1505	1510	1515	4560
acg tgc cgc cct gga gcc aca gga agg aag tgt gat ggc tgc gag cac	Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp Gly Cys Glu His	1525	1530	1535	4608
tgg cat gca cgc gag ggt gca gag tgt gtc ttt tgt gga gac gag tgt	Trp His Ala Arg Glu Gly Ala Glu Cys Val Phe Cys Gly Asp Glu Cys	1540	1545	1550	4656
aca ggc ctt ctt ctt ggt gac ctg gct cgt cta gag cag atg acc atg	Thr Gly Leu Leu Leu Gly Asp Leu Ala Arg Leu Glu Gln Met Thr Met	1555	1560	1565	4704
aac atc aac ctc acg ggc cca ctg cct gct cca tat aaa att ctg tat	Asn Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr Lys Ile Leu Tyr	1570	1575	1580	4752
ggt ctt gaa aat aca act cag gaa ctc aag cac ctg cta tca ccg caa	Gly Leu Glu Asn Thr Thr Gln Glu Leu Lys His Leu Leu Ser Pro Gln	1585	1590	1595	4800
cgg gca cca gag agg ctc att cag ttg gca gag ggc aac gtg aac aca	Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly Asn Val Asn Thr	1605	1610	1615	4848
ctt gtg atg gaa aca aat gag ctg cta acc aga gca acc aaa gtg aca	Leu Val Met Glu Thr Asn Glu Leu Leu Thr Arg Ala Thr Lys Val Thr	1620	1625	1630	4896
gca gat ggt gag caa aca gga caa gat gct gag agg acc aac tcc aga	Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg Thr Asn Ser Arg	1635	1640	1645	4944
gca gaa tcc ttg gaa gaa ttc att aaa ggg ctt gtc cag gat gct gaa	Ala Glu Ser Leu Glu Glu Phe Ile Lys Gly Leu Val Gln Asp Ala Glu	1650	1655	1660	4992
gcc ata aat gaa aaa gct gta aaa cta aat gaa acc tta gga aat caa	Ala Ile Asn Glu Lys Ala Val Lys Leu Asn Glu Thr Leu Gly Asn Gln				5040

1665	1670	1675	1680	
gat aag aca gca gag aga aac ttg gag gag ctt caa aag gaa atc gac				5088
Asp Lys Thr Ala Glu Arg Asn Leu Glu Glu Leu Gln Lys Glu Ile Asp	1685	1690	1695	
cgg atg ctg aag gaa ctg aga agt aaa gat ctt caa aca cag aag gaa				5136
Arg Met Leu Lys Glu Leu Arg Ser Lys Asp Leu Gln Thr Gln Lys Glu	1700	1705	1710	
gtt gct gag gat gag ctc gtg gca gca gaa ggc ctt ctg aag aga gta				5184
Val Ala Glu Asp Glu Leu Val Ala Ala Glu Gly Leu Leu Lys Arg Val	1715	1720	1725	
aac aag ctg ttt gga gag ccc aga gcc cag aat gaa gat atg gaa aag				5232
Asn Lys Leu Phe Gly Glu Pro Arg Ala Gln Asn Glu Asp Met Glu Lys	1730	1735	1740	
gat ctc cag cag aaa ctg gca gag tac aag aac aaa ctt gat gat gct				5280
Asp Leu Gln Gln Lys Leu Ala Glu Tyr Lys Asn Lys Leu Asp Asp Ala	1745	1750	1755	1760
tggt gat cta ttg aga gaa gcc act gat aaa acc cga gat gct aat cgt				5328
Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Thr Arg Asp Ala Asn Arg	1765	1770	1775	
ttg tct gct gcc aat caa aaa aac atg acc ata ctg gag aca aag aag				5376
Leu Ser Ala Ala Asn Gln Lys Asn Met Thr Ile Leu Glu Thr Lys Lys	1780	1785	1790	
gag gct att gaa ggt agc aaa cga caa ata gag aac act tta aag gaa				5424
Glu Ala Ile Glu Gly Ser Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu	1795	1800	1805	
ggc aat gac atc ctt gat gaa gcc aat caa ctc tta ggt gaa atc aac				5472
Gly Asn Asp Ile Leu Asp Glu Ala Asn Gln Leu Leu Gly Glu Ile Asn	1810	1815	1820	
tca gtc ata gat tat gtc gac gac att aaa act aag ttg cca cca atg				5520
Ser Val Ile Asp Tyr Val Asp Asp Ile Lys Thr Lys Leu Pro Pro Met	1825	1830	1835	1840
tcc gag gag ctg agt gac aaa ata gat gac ctc gcc cag gaa ata aag				5568
Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp Leu Ala Gln Glu Ile Lys	1845	1850	1855	
gac aga agg ctt gct gag aag gtg ttc cag gct gag agc cat gct gct				5616
Asp Arg Arg Leu Ala Glu Lys Val Phe Gln Ala Glu Ser His Ala Ala	1860	1865	1870	
cag ctg aac gac tcg tct gct gta ctt gat gga atc ctg gat gag gct				5664
Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile Leu Asp Glu Ala	1875	1880	1885	
aag aac atc tct ttc aat gcc acg gca gcc ttc aga gct tac agt aat				5712
Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Arg Ala Tyr Ser Asn	1890	1895	1900	
att aaa gac tac att gat gaa gct gag aaa gtg gcc aga gaa gcc aaa				5760
Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala Arg Glu Ala Lys	1905	1910	1915	1920

gag ctt gcc caa ggg gct aca aaa ctg gca aca agt cct cag ggc tta	5808
Glu Leu Ala Gln Gly Ala Thr Lys Leu Ala Thr Ser Pro Gln Gly Leu	
1925 1930 1935	
tta aaa gaa gat gcc aaa ggc tcc ctt cag aaa agc ttc agg atc ctc	5856
Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln Lys Ser Phe Arg Ile Leu	
1940 1945 1950	
aat gaa gcc aag aag cta gca aac gat gtg aaa gga aat cac aat gat	5904
Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Gly Asn His Asn Asp	
1955 1960 1965	
cta aat gac ctg aaa acc agg tta gaa act gct gac ctt aga aac agt	5952
Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr Ala Asp Leu Arg Asn Ser	
1970 1975 1980	
gga ctt cta gga gct cta aat gac acc atg gac aag tta tca gcc att	6000
Gly Leu Leu Gly Ala Leu Asn Asp Thr Met Asp Lys Leu Ser Ala Ile	
1985 1990 1995 2000	
aca aat gac acg gct gct aaa ctg cag gct gtc aaa gag aaa gcc aga	6048
Thr Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys Glu Lys Ala Arg	
2005 2010 2015	
gaa gcc aat gac aca gca aaa gct gtc ctg gcc cag gtt aag gac ctg	6096
Glu Ala Asn Asp Thr Ala Lys Ala Val Leu Ala Gln Val Lys Asp Leu	
2020 2025 2030	
cat cag aac cta gat ggc ctg aag caa aac tac aat aaa ctg gca gac	6144
His Gln Asn Leu Asp Gly Leu Lys Gln Asn Tyr Asn Lys Leu Ala Asp	
2035 2040 2045	
agc gtg gcc aaa acg aac gct gtg gtg aaa gat cct tcc aaa aac aaa	6192
Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro Ser Lys Asn Lys	
2050 2055 2060	
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Ile Ile Ala Asp Ala Gly Thr Ser Val Arg Asn Leu Glu Gln Glu Ala	
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Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg	
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Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser Gly Gly Asp Cys	
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Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile	
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Val Val His Val Lys Thr Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu	
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Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr Arg Ile Glu Ala	
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Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe Met Ser Val Glu Leu Ser	
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 Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val Glu His Val Pro
 35 40 45
 Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser
 50 55 60
 Ser Asn Pro Tyr Gln Arg His Pro Ile Thr Asn Ala Ile Asp Gly Lys
 65 70 75 80
 Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly Val Glu Tyr His
 85 90 95
 Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr
 100 105 110
 Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu
 115 120 125
 Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp Gln Tyr His Ala
 130 135 140
 Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr
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 Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile Cys Thr Ser Phe
 165 170 175
 Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile His Ile Ser Leu
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 Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu
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 Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr
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 Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp Pro Arg Glu Ile
 225 230 235 240
 Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser
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 Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg Ala Cys Pro Leu
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 Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys
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 Gly Glu Ser Cys Asp Arg Cys Cys Pro Gly Phe His Gln Lys Pro Trp
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 Arg Ala Gly Thr Phe Leu Thr Lys Ser Glu Cys Glu Ala Cys Asn Cys
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His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Thr Val Ala Ser Arg
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 Asn Leu Ser Leu Asn Ile His Gly Lys Tyr Ile Gly Gly Gly Val Cys
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 Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro Cys Asn Cys Ser Gly Leu
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 Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg
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Cys Asn Glu His Ser Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu 340 345 350		
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Glu	Cys	Asp	Pro	Gln	Gly	Ser	Leu	Ser	Ser	Val	Cys	Asp	Pro	Asn	Gly	
		755					760					765				
ggc	cag	tgc	cag	tgc	cgg	ccc	aac	gtg	gtt	gga	aga	acc	tgc	aac	aga	2352
Gly	Gln	Cys	Gln	Cys	Arg	Phe	Gly	Pro	Asn	Val	Val	Gly	Arg	Thr	Cys	
	770						775					780				
tgt	gca	cct	gga	act	ttt	ggc	ttt	ggc	ccc	agt	gga	tgc	aaa	cct	tgt	2400
Cys	Ala	Pro	Gly	Thr	Phe	Gly	Phe	Gly	Pro	Ser	Gly	Cys	Lys	Pro	Cys	
	785				790					795				800		
gag	tgc	cat	ctg	caa	gga	tct	gtc	aat	gcc	ttc	tgc	aat	ccc	gtc	act	2448
Glu	Cys	His	Leu	Gln	Gly	Ser	Val	Asn	Ala	Phe	Cys	Asn	Pro	Val	Thr	
			805						810					815		
ggc	cag	tgc	cac	tgt	ttc	cag	gga	gtg	tat	gct	cgg	cag	tgt	gat	cgg	2496
Gly	Gln	Cys	His	Cys	Phe	Gln	Gly	Val	Tyr	Ala	Arg	Gln	Cys	Asp	Arg	
			820					825					830			
tgc	tta	cct	ggg	cac	tgg	ggc	ttt	cca	agt	tgc	cag	ccc	tgc	cag	tgc	2544
Cys	Leu	Pro	Gly	His	Trp	Gly	Phe	Pro	Ser	Cys	Gln	Pro	Cys	Gln	Cys	
		835					840					845				
aat	ggc	cac	gcc	gat	gac	tgc	gac	cca	gtg	act	ggg	gag	tgc	ttg	aac	2592
Asn	Gly	His	Ala	Asp	Asp	Cys	Asp	Pro	Val	Thr	Gly	Glu	Cys	Leu	Asn	
	850					855					860					
tgc	cag	gac	tac	acc	atg	ggc	cat	aac	tgt	gaa	agg	tgc	ttg	gct	ggc	2640
Cys	Gln	Asp	Tyr	Thr	Met	Gly	His	Asn	Cys	Glu	Arg	Cys	Leu	Ala	Gly	
	865				870					875				880		
tac	tat	ggc	gac	ccc	atc	att	ggg	tca	ggc	gat	cac	tgc	cgc	cct	tgc	2688
Tyr	Tyr	Gly	Asp	Pro	Ile	Ile	Gly	Ser	Gly	Asp	His	Cys	Arg	Pro	Cys	
			885						890					895		
cct	tgc	cca	gat	ggc	ccc	gac	agt	gga	cgc	cag	ttt	gcc	agg	agc	tgc	2736
Pro	Cys	Pro	Asp	Gly	Pro	Asp	Ser	Gly	Arg	Gln	Phe	Ala	Arg	Ser	Cys	
		900						905					910			
tac	caa	gat	cct	ggt	act	tta	cag	ctt	gcc	tgt	ggt	tgt	gat	cct	gga	2784
Tyr	Gln	Asp	Pro	Val	Thr	Leu	Gln	Leu	Ala	Cys	Val	Cys	Asp	Pro	Gly	
	915						920					925				
tac	att	ggc	tcc	aga	tgt	gac	gac	tgt	gcc	tca	gga	tac	ttt	ggc	aac	2832
Tyr	Ile	Gly	Ser	Arg	Cys	Asp	Asp	Cys	Ala	Ser	Gly	Tyr	Phe	Gly	Asn	
	930					935					940					
cca	tca	gaa	gtt	ggg	ggg	tgc	tgt	cag	cct	tgc	cag	tgt	cac	aac	aac	2880
Pro	Ser	Glu	Val	Gly	Gly	Ser	Cys	Gln	Pro	Cys	Gln	Cys	His	Asn	Asn	
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att	gac	acg	aca	gac	cca	gaa	gcc	tgt	gac	aag	gag	act	ggg	agg	tgt	2928
Ile	Asp	Thr	Thr	Asp	Pro	Glu	Ala	Cys	Asp	Lys	Glu	Thr	Gly	Arg	Cys	

	965	970	975	
ctc aag tgc ctg tac cac acg gaa ggg gaa cac tgt cag ttc tgc cgg				2976
Leu Lys Cys Leu Tyr His Thr Glu Gly Glu His Cys Gln Phe Cys Arg	980	985	990	
ttt gga tac tat ggt gat gcc ctc cgg cag gac tgt cga aag tgt gtc				3024
Phe Gly Tyr Tyr Gly Asp Ala Leu Arg Gln Asp Cys Arg Lys Cys Val	995	1000	1005	
tgt aat tac ctg ggc acc gtg caa gag cac tgt aac ggc tct gac tgc				3072
Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys Asn Gly Ser Asp Cys	1010	1015	1020	
cag tgc gac aaa gcc act ggt cag tgc ttg tgt ctt cct aat gtg atc				3120
Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys Leu Pro Asn Val Ile	1025	1030	1035	1040
ggg cag aac tgt gac cgc tgt gcg ccc aat acc tgg cag ctg gcc agt				3168
Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr Trp Gln Leu Ala Ser	1045	1050	1055	
ggc act ggc tgt gac cca tgc aac tgc aat gct gct cat tcc ttc ggg				3216
Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala Ala His Ser Phe Gly	1060	1065	1070	
cca tct tgc aat gag ttc acg ggg cag tgc cag tgc atg cct ggg ttt				3264
Pro Ser Cys Asn Glu Phe Thr Gly Gln Cys Gln Cys Met Pro Gly Phe	1075	1080	1085	
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Gly Gly Arg Thr Cys Ser Glu Cys Gln Glu Leu Phe Trp Gly Asp Pro	1090	1095	1100	
gac gtg gag tgc cga gcc tgt gac tgt gac ccc agg ggc att gag acg				3360
Asp Val Glu Cys Arg Ala Cys Asp Cys Asp Pro Arg Gly Ile Glu Thr	1105	1110	1115	1120
cca cag tgt gac cag tcc acg ggc cag tgt gtc tgc gtt gag ggt gtt				3408
Pro Gln Cys Asp Gln Ser Thr Gly Gln Cys Val Cys Val Glu Gly Val	1125	1130	1135	
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Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly Tyr Ser Gly Val Phe	1140	1145	1150	
cct gac tgc aca ccc tgc cac cag tgc ttt gct ctc tgg gat gtg atc				3504
Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala Leu Trp Asp Val Ile	1155	1160	1165	
att gcc gag ctg acc aac agg aca cac aga ttc ctg gag aaa gcc aag				3552
Ile Ala Glu Leu Thr Asn Arg Thr His Arg Phe Leu Glu Lys Ala Lys	1170	1175	1180	
gcc ttg aag atc agt ggt gtg atc ggg cct tac cgt gag act gtg gac				3600
Ala Leu Lys Ile Ser Gly Val Ile Gly Pro Tyr Arg Glu Thr Val Asp	1185	1190	1195	1200
tcg gtg gag agg aaa gtc agc gag ata aaa gac atc ctg gcg cag agc				3648
Ser Val Glu Arg Lys Val Ser Glu Ile Lys Asp Ile Leu Ala Gln Ser	1205	1210	1215	

ccc gca gca gag cca ctg aaa aac att ggg aat ctc ttt gag gaa gca 3696
 Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Asn Leu Phe Glu Glu Ala
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gag aaa ctg att aaa gat gtt aca gaa atg atg gct caa gta gaa gtg 3744
 Glu Lys Leu Ile Lys Asp Val Thr Glu Met Met Ala Gln Val Glu Val
 1235 1240 1245

aaa tta tct gac aca act tcc caa agc aac agc aca gcc aaa gaa ctg 3792
 Lys Leu Ser Asp Thr Thr Ser Asn Ser Thr Ala Lys Glu Leu
 1250 1255 1260

gat tct cta cag aca gaa gcc gaa agc cta gac aac act gtg aaa gaa 3840
 Asp Ser Leu Gln Thr Glu Ala Glu Ser Leu Asp Asn Thr Val Lys Glu
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 Leu Ala Glu Gln Leu Glu Phe Ile Lys Asn Ser Asp Ile Arg Gly Ala
 1285 1290 1295

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 Leu Asp Ser Ile Thr Lys Tyr Phe Gln Met Ser Leu Glu Ala Glu Glu
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 Arg Val Asn Ala Ser Thr Thr Glu Pro Asn Ser Thr Val Glu Gln Ser
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gcc ctc atg aga gac aga gta gaa gac gtg atg atg gag cga gaa tcc 4032
 Ala Leu Met Arg Asp Arg Val Glu Asp Val Met Met Glu Arg Glu Ser
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 Cys Gly Thr Pro Pro Gly Ala Ser Cys Ser Glu Thr Glu Cys Gly Gly
 1380 1385 1390

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 Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys Cys Gly Gly Pro Gly
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 Asp Leu Asp Gln Asp Val Leu Ser Ala Leu Ala Glu Val Glu Gln Leu
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 Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala Asp Glu Ala Lys Gln
 1445 1450 1455

agt gct gaa gac att ctg ttg aag aca aat gct acc aaa gaa aaa atg 4416
 Ser Ala Glu Asp Ile Leu Leu Lys Thr Asn Ala Thr Lys Glu Lys Met
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 Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile Lys Gln Ile Arg Asn
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 Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser Ile Glu Ala Val Ala
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 Val Thr Ala Asp Met Val Lys Glu Ala Leu Glu Glu Ala Glu Lys Ala
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 Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu Lys Tyr Lys Lys Val
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Lys Ala Glu Met Leu Gln Asn Glu Ala Lys Thr Leu Leu Ala Gln Ala
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 <213> Homo sapiens

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 20 25 30
 Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr Cys Ile Val Ser His
 35 40 45
 Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn Ser Gln Asp Pro Tyr
 50 55 60
 His Glu Thr Leu Asn Pro Asp Ser His Leu Ile Glu Asn Val Val Thr
 65 70 75 80
 Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp Gln Ser Glu Asn Gly
 85 90 95
 Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His Phe
 100 105 110
 Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu
 115 120 125
 Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp Gly Val Tyr Arg Tyr
 130 135 140
 Phe Ala Tyr Asp Cys Glu Ala Ser Phe Pro Gly Ile Ser Thr Gly Pro
 145 150 155 160
 Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser Arg Tyr Ser Asp Ile

165										170				175			
Glu	Pro	Ser	Thr 180	Glu	Gly	Glu	Val	Ile 185	Phe	Arg	Ala	Leu	Asp 190	Pro	Ala		
Phe	Lys	Ile 195	Glu	Asp	Pro	Tyr	Ser 200	Pro	Arg	Ile	Gln	Asn 205	Leu	Leu	Lys		
Ile	Thr 210	Asn	Leu	Arg	Ile	Lys 215	Phe	Val	Lys	Leu	His 220	Thr	Leu	Gly	Asp		
Asn 225	Leu	Leu	Asp	Ser	Arg 230	Met	Glu	Ile	Arg	Glu 235	Lys	Tyr	Tyr	Tyr	Ala 240		
Val	Tyr	Asp	Met	Val 245	Val	Arg	Gly	Asn	Cys 250	Phe	Cys	Tyr	Gly	His 255	Ala		
Ser	Glu	Cys	Ala 260	Pro	Val	Asp	Gly	Phe 265	Asn	Glu	Glu	Val	Glu	Gly	Met		
Val	His	Gly 275	His	Cys	Met	Cys	Arg 280	His	Asn	Thr	Lys	Gly 285	Leu	Asn	Cys		
Glu	Leu 290	Cys	Met	Asp	Phe	Tyr 295	His	Asp	Leu	Pro	Trp 300	Arg	Pro	Ala	Glu		
Gly 305	Arg	Asn	Ser	Asn	Ala 310	Cys	Lys	Lys	Cys	Asn 315	Cys	Asn	Glu	His	Ser 320		
Ile	Ser	Cys	His	Phe 325	Asp	Met	Ala	Val	Tyr 330	Leu	Ala	Thr	Gly	Asn 335	Val		
Ser	Gly	Gly	Val 340	Cys	Asp	Asp	Cys	Gln	His 345	Asn	Thr	Met	Gly	Arg	Asn		
Cys	Glu	Gln 355	Cys	Lys	Pro	Phe	Tyr 360	Tyr	Gln	His	Pro	Glu 365	Arg	Asp	Ile		
Arg 370	Asp	Pro	Asn	Phe	Cys	Glu 375	Arg	Cys	Thr	Cys	Asp 380	Pro	Ala	Gly	Ser		
Gln 385	Asn	Glu	Gly	Ile	Cys 390	Asp	Ser	Tyr	Thr	Asp 395	Phe	Ser	Thr	Gly	Leu 400		
Ile	Ala	Gly	Gln	Cys 405	Arg	Cys	Lys	Leu	Asn 410	Val	Glu	Gly	Glu	His 415	Cys		
Asp	Val	Cys	Lys 420	Glu	Gly	Phe	Tyr	Asp 425	Leu	Ser	Ser	Glu	Asp 430	Pro	Phe		
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Asn 450	Pro	Cys	Asp	Ser	Glu	Thr 455	Gly	His	Cys	Tyr	Cys 460	Lys	Arg	Leu	Val		
Thr 465	Gly	Gln	His	Cys	Asp 470	Gln	Cys	Leu	Pro	Glu 475	His	Trp	Gly	Leu	Ser 480		
Asn	Asp	Leu	Asp	Gly 485	Cys	Arg	Pro	Cys	Asp 490	Cys	Asp	Leu	Gly	Gly	Ala 495		

Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln Cys Ser Cys Arg Pro
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 His Met Ile Gly Arg Gln Cys Asn Glu Val Glu Pro Gly Tyr Tyr Phe
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 Ala Thr Leu Asp His Tyr Leu Tyr Glu Ala Glu Glu Ala Asn Leu Gly
 530 535 540
 Pro Gly Val Ser Ile Val Glu Arg Gln Tyr Ile Gln Asp Arg Ile Pro
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 Ser Trp Thr Gly Ala Gly Phe Val Arg Val Pro Glu Gly Ala Tyr Leu
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 Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met Glu Tyr Asp Ile Leu
 580 585 590
 Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp Glu Lys Ala Val Ile
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 Thr Val Gln Arg Pro Gly Arg Ile Pro Thr Ser Ser Arg Cys Gly Asn
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 Thr Ile Pro Asp Asp Asp Asn Gln Val Val Ser Leu Ser Pro Gly Ser
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 645 650 655
 Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr Ser Ser Asp Ser Asp
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 Val Glu Ser Pro Tyr Thr Leu Ile Asp Ser Leu Val Leu Met Pro Tyr
 675 680 685
 Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly Ser Gly Asp Gly Val
 690 695 700
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 Asn Ser Arg Ser Val Val Lys Thr Pro Met Thr Asp Val Cys Arg Asn
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 Ile Ile Phe Ser Ile Ser Ala Leu Leu His Gln Thr Gly Leu Ala Cys
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 Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val Cys Asp Pro Asn Gly
 755 760 765
 Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly Arg Thr Cys Asn Arg
 770 775 780
 Cys Ala Pro Gly Thr Phe Gly Phe Gly Pro Ser Gly Cys Lys Pro Cys
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Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala Arg Gln Cys Asp Arg
 820 825 830
 Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys Gln Pro Cys Gln Cys
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 Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr Gly Glu Cys Leu Asn
 850 855 860
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 Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp His Cys Arg Pro Cys
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 Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln Phe Ala Arg Ser Cys
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 Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys Val Cys Asp Pro Gly
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 Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser Gly Tyr Phe Gly Asn
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 Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys Gln Cys His Asn Asn
 945 950 955 960
 Ile Asp Thr Thr Asp Pro Glu Ala Cys Asp Lys Glu Thr Gly Arg Cys
 965 970 975
 Leu Lys Cys Leu Tyr His Thr Glu Gly Glu His Cys Gln Phe Cys Arg
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Pro Asp Cys Thr	Pro Cys His Gln Cys Phe Ala Leu Trp	Asp Val Ile
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Ile Ala Glu Leu Thr Asn Arg Thr His Arg Phe Leu Glu Lys Ala Lys		
1170	1175	1180
Ala Leu Lys Ile Ser Gly Val Ile Gly Pro Tyr Arg Glu Thr Val Asp		
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Ser Val Glu Arg Lys Val Ser Glu Ile Lys Asp Ile Leu Ala Gln Ser		
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Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Asn Leu Phe Glu Glu Ala		
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Glu Lys Leu Ile Lys Asp Val Thr Glu Met Met Ala Gln Val Glu Val		
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Lys Leu Ser Asp Thr Thr Ser Gln Ser Asn Ser Thr Ala Lys Glu Leu		
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Ala Leu Met Arg Asp Arg Val Glu Asp Val Met Met Glu Arg Glu Ser		
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Cys Gly Gly Leu Val Thr Val Ala His Asn Ala Trp Gln Lys Ala Met		
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Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Ser Ala	1425	1430	1435
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 His Leu Ile Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys
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Phe	Pro	Gly 115	Ile	Ser	Thr	Gly	Pro 120	Met	Lys	Lys	Val	Asp 125	Asp	Ile	Ile
Cys	Asp 130	Ser	Arg	Tyr	Ser	Asp 135	Ile	Glu	Pro	Ser	Thr 140	Glu	Gly	Glu	Val
Ile 145	Phe	Arg	Ala	Leu	Asp 150	Pro	Ala	Phe	Lys	Ile 155	Glu	Asp	Pro	Tyr	Ser 160
Pro	Arg	Ile	Gln	Asn 165	Leu	Leu	Lys	Ile	Thr 170	Asn	Leu	Arg	Ile	Lys 175	Phe
Val	Lys	Leu	His 180	Thr	Leu	Gly	Asp	Asn 185	Leu	Leu	Asp	Ser	Arg 190	Met	Glu
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 Pro Met Thr Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu
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Arg Pro Ala Leu Thr Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu	
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acc tct atc aag ata cgt ggg aca tac agt gag aga agt gct gga tat	2260
Thr Ser Ile Lys Ile Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr	
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Leu Asp Val Thr Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro	
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Ala Thr Trp Val Glu Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln	
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Phe Cys Glu Met Cys Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu	
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Gly Pro Tyr Ser Pro Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu	
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Gly Pro His Cys Glu Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr	
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Ala Gly Thr Ser Ser Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser	
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Ser Cys Ala Val Val Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys	
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Pro Thr Gly Thr Thr Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr	
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Cys Gln Cys Ser Asp Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn	
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Tyr Cys Asp Arg Cys Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro	
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Asn Pro Ala Asp Lys Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr	
880 885 890	
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Met Lys Gln Gln Ser Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys	
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Leu Pro His Val Thr Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe	
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Tyr Asn Leu Gln Ser Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala	
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Leu Gly Ser Thr Asn Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu	
940 945 950 955	
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Cys Gln Pro Gly Ile Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn	
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Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe	
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Lys Thr Arg Glu Ala Gln Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala			
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Leu Gln Glu Ala Glu Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp			
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Gln Asp Met Met Met Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala			
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Ile Ile Asn Asp Leu Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp			
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 Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val
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 Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr
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 Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln
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 Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln
 100 105 110
 Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln
 115 120 125
 Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp
 130 135 140
 Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe
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 Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln
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 Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly
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 Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu

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Asn	Thr	Phe	Gly	Asp	Glu	Val	Phe	Asn	Asp	Pro	Lys	Val	Leu	Lys	Ser
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Tyr	Tyr	Tyr	Ala	Ile	Ser	Asp	Phe	Ala	Val	Gly	Gly	Arg	Cys	Lys	Cys
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Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met 1475	1480	1485
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 Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile
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Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala	
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Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr	
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Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe	
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Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe	
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Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu	
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Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn	
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Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu Asn	
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Pro	Val	Gly	Ser	Leu	Ser	Thr	Gln	Cys	Asp	Ser	Tyr	Gly	Arg	Cys	Ser		
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Cys	Lys	Pro	Gly	Val	Met	Gly	Asp	Lys	Cys	Asp	Arg	Cys	Gln	Pro	Gly		
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Phe	His	Ser	Leu	Thr	Glu	Ala	Gly	Cys	Arg	Pro	Cys	Ser	Cys	Asp	Pro		
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Ser	Gly	Ser	Ile	Asp	Glu	Cys	Asn	Val	Glu	Thr	Gly	Arg	Cys	Val	Cys		
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Lys	Asp	Asn	Val	Glu	Gly	Phe	Asn	Cys	Glu	Arg	Cys	Lys	Pro	Gly	Phe		
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Phe	Asn	Leu	Glu	Ser	Ser	Asn	Pro	Arg	Gly	Cys	Thr	Pro	Cys	Phe	Cys		
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Phe	Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	Val	Tyr		
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Ser	Ile	Ser	Ser	Thr	Phe	Gln	Ile	Asp	Glu	Asp	Gly	Trp	Arg	Ala	Glu		
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cag	aga	gat	ggc	tct	gaa	gca	tct	ctc	gag	tgg	tcc	tct	gag	agg	caa	1536	
Gln	Arg	Asp	Gly	Ser	Glu	Ala	Ser	Leu	Glu	Trp	Ser	Ser	Glu	Arg	Gln		
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gat	atc	gcc	gtg	atc	tca	gac	agc	tac	ttt	cct	cgg	tac	ttc	att	gct	1584	
Asp	Ile	Ala	Val	Ile	Ser	Asp	Ser	Tyr	Phe	Pro	Arg	Tyr	Phe	Ile	Ala		
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cct	gca	aag	ttc	ttg	ggc	aag	cag	gtg	ttg	agt	tat	ggg	cag	aac	ctc	1632	
Pro	Ala	Lys	Phe	Leu	Gly	Lys	Gln	Val	Leu	Ser	Tyr	Gly	Gln	Asn	Leu		
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Ala	Gln	Gly	Asn	Ser	Tyr	Pro	Ser	Glu	Thr	Thr	Val	Lys	Tyr	Val	Phe		
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Arg	Leu	His	Glu	Ala	Thr	Asp	Tyr	Pro	Trp	Arg	Pro	Ala	Leu	Thr	Pro		

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1570

1575

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 Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly
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 Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser Gly

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 Met Arg Gly Ser His Arg Ala Ala Pro Ala Leu
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 Arg Pro Arg Gly Arg Leu Trp Pro Val Leu Ala Val Leu Ala Ala Ala
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 Ala Ala Ala Gly Cys Ala Gln Ala Ala Met Asp Glu Cys Thr Asp Glu
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 Gly Gly Arg Pro Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe
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 aac gtg act gtg gtg gcc acc aac acg tgt ggg act ccg ccc gag gaa 484
 Asn Val Thr Val Val Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu
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 tac tgt gtg cag acc ggg gtg acc ggg gtc acc aag tcc tgt cac ctg 532
 Tyr Cys Val Gln Thr Gly Val Thr Gly Val Thr Lys Ser Cys His Leu
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 tgc gac gcc ggg cag ccc cac ctg cag cac ggg gca gcc ttc ctg acc 580

Cys	Asp	Ala	Gly	Gln	Pro	His	Leu	Gln	His	Gly	Ala	Ala	Phe	Leu	Thr		
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gac	tac	aac	aac	cag	gcc	gac	acc	acc	tgg	tgg	caa	agc	cag	acc	atg	628	
Asp	Tyr	Asn	Asn	Gln	Ala	Asp	Thr	Thr	Trp	Trp	Gln	Ser	Gln	Thr	Met		
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ctg	gcc	ggg	gtg	cag	tac	ccc	agc	tcc	atc	aac	ctc	acg	ctg	cac	ctg	676	
Leu	Ala	Gly	Val	Gln	Tyr	Pro	Ser	Ser	Ile	Asn	Leu	Thr	Leu	His	Leu		
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gga	aaa	gct	ttt	gac	atc	acc	tat	gtg	cgt	ctc	aag	ttc	cac	acc	agc	724	
Gly	Lys	Ala	Phe	Asp	Ile	Thr	Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser		
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cgc	ccg	gag	agc	ttt	gcc	att	tac	aag	cgc	aca	cgg	gaa	gac	ggg	ccc	772	
Arg	Pro	Glu	Ser	Phe	Ala	Ile	Tyr	Lys	Arg	Thr	Arg	Glu	Asp	Gly	Pro		
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Trp	Ile	Pro	Tyr	Gln	Tyr	Tyr	Ser	Gly	Ser	Cys	Glu	Asn	Thr	Tyr	Ser		
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Lys	Ala	Asn	Arg	Gly	Phe	Ile	Arg	Thr	Gly	Gly	Asp	Glu	Gln	Gln	Ala		
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ttg	tgt	act	gat	gaa	ttc	agt	gac	att	tct	ccc	ctc	act	ggg	ggc	aac	916	
Leu	Cys	Thr	Asp	Glu	Phe	Ser	Asp	Ile	Ser	Pro	Leu	Thr	Gly	Gly	Asn		
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gtg	gcc	ttt	tct	acc	ctg	gaa	gga	agg	ccc	agc	gcc	tat	aac	ttt	gac	964	
Val	Ala	Phe	Ser	Thr	Leu	Glu	Gly	Arg	Pro	Ser	Ala	Tyr	Asn	Phe	Asp		
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aat	agc	cct	gtg	ctg	cag	gaa	tgg	gta	act	gcc	act	gac	atc	aga	gta	1012	
Asn	Ser	Pro	Val	Leu	Gln	Glu	Trp	Val	Thr	Ala	Thr	Asp	Ile	Arg	Val		
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act	ctt	aat	cgc	ctg	aac	act	ttt	gga	gat	gaa	gtg	ttt	aac	gat	ccc	1060	
Thr	Leu	Asn	Arg	Leu	Asn	Thr	Phe	Gly	Asp	Glu	Val	Phe	Asn	Asp	Pro		
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aaa	gtt	ctc	aag	tcc	tat	tat	tat	gcc	atc	tct	gat	ttt	gct	gta	ggg	1108	
Lys	Val	Leu	Lys	Ser	Tyr	Tyr	Tyr	Ala	Ile	Ser	Asp	Phe	Ala	Val	Gly		
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ggc	aga	tgt	aaa	tgt	aat	gga	cac	gca	agc	gag	tgt	atg	aag	aac	gaa	1156	
Gly	Arg	Cys	Lys	Cys	Asn	Gly	His	Ala	Ser	Glu	Cys	Met	Lys	Asn	Glu		
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Phe	Asp	Lys	Leu	Val	Cys	Asn	Cys	Lys	His	Asn	Thr	Tyr	Gly	Val	Asp		
	300				305					310				315			
tgt	gaa	aag	tgt	ctt	cct	ttc	ttc	aat	gac	cgg	ccg	tgg	agg	agg	gca	1252	
Cys	Glu	Lys	Cys	Leu	Pro	Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala		
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Thr	Ala	Glu	Ser	Ala	Ser	Glu	Cys	Leu	Pro	Cys	Asp	Cys	Asn	Gly	Arg		

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Ser Gln Glu Cys Tyr Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His			
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Gly Gly His Cys Thr Asn Cys Gln Asp Asn Thr Asp Gly Ala His Cys			
365	370	375	
gag agg tgc cga gag aac ttc ttc cgc ctt ggc aac aat gaa gcc tgc			1444
Glu Arg Cys Arg Glu Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys			
380	385	390	395
tct tca tgc cac tgt agt cct gtg ggc tct cta agc aca cag tgt gat			1492
Ser Ser Cys His Cys Ser Pro Val Gly Ser Leu Ser Thr Gln Cys Asp			
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Ser Tyr Gly Arg Cys Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys			
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gac cgt tgc cag cct gga ttc cat tct ctc act gaa gca gga tgc agg			1588
Asp Arg Cys Gln Pro Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg			
430	435	440	
cca tgc tct tgt gat ccc tct ggc agc ata gat gaa tgt aat gtt gaa			1636
Pro Cys Ser Cys Asp Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu			
445	450	455	
aca gga aga tgt gtt tgc aaa gac aat gtc gaa ggc ttc aat tgt gaa			1684
Thr Gly Arg Cys Val Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu			
460	465	470	475
aga tgc aaa cct gga ttt ttt aat ctg gaa tca tct aat cct cgg ggt			1732
Arg Cys Lys Pro Gly Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly			
480	485	490	
tgc aca ccc tgc ttc tgc ttt ggg cat tct tct gtc tgt aca aac gct			1780
Cys Thr Pro Cys Phe Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala			
495	500	505	
gtt ggc tac agt gtt tat tct atc tcc tct acc ttt cag att gat gag			1828
Val Gly Tyr Ser Val Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu			
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gat ggg tgg cgt gcg gaa cag aga gat ggc tct gaa gca tct ctc gag			1876
Asp Gly Trp Arg Ala Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu			
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Trp Ser Ser Glu Arg Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe			
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cct cgg tac ttc att gct cct gca aag ttc ttg ggc aag cag gtg ttg			1972
Pro Arg Tyr Phe Ile Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu			
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agt tat ggt cag aac ctc tcc ttc tcc ttt cga gtg gac agg cga gat			2020
Ser Tyr Gly Gln Asn Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp			
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Thr Arg Leu Ser Ala Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg	
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Val Ser Val Pro Leu Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr	
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Thr Val Lys Tyr Val Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp	
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Arg Pro Ala Leu Thr Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu	
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Thr Ser Ile Lys Ile Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr	
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Leu Asp Asp Val Thr Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro	
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Ala Thr Trp Val Glu Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln	
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Phe Cys Glu Met Cys Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu	
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Gly Pro His Cys Glu Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr	
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Ala Gly Thr Ser Ser Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser	
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Ser Cys Ala Val Val Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys	
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Pro Thr Gly Thr Thr Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr	
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Cys Gln Cys Ser Asp Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn	
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Tyr Cys Asp Arg Cys Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro	
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Asp Gln Ala Phe Glu Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met	
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Asp Leu Leu Arg Glu Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu	
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Met Asp Arg Leu Gln Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser	
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Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg	
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cta agg aag att cct gcc atc aac cag acc atc act gaa gcc aat gaa			4468
Leu Arg Lys Ile Pro Ala Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu			
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Lys Thr Arg Glu Ala Gln Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala			
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aca gag gcc aag aac aag gcc cat gag gcc gag agg atc gca agc gct			4564
Thr Glu Ala Lys Asn Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala			
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gtc caa aag aat gcc acc agc acc aag gca gaa gct gaa aga act ttt			4612
Val Gln Lys Asn Ala Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe			
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gca gaa gtt aca gat ctg gat aat gag gtg aac aat atg ttg aag caa			4660
Ala Glu Val Thr Asp Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln			
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Gln Asp Met Met Met Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala			
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Glu Ile Asn Ala Arg Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser			
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att att aat gac ctc ttg gag cag ctg ggg cag ctg gat aca gtg gac			4852
Ile Ile Asn Asp Leu Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp			
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 Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val
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 Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr
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 Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln
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 Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln
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 Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln
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 Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp
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 Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe
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 Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu
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 Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu
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 Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly
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Cys	Lys	Ala	Cys	Asn	Cys	Asn	Pro	Tyr	Gly	Thr	Met	Lys	Gln	Gln	Ser
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Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys	1380	1385	1390	
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Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu Lys	1425	1430	1435	1440
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Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala	1445	1450	1455	
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Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro
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His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala
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Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr
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Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile
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Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala
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Leu	Pro	Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala	Thr	Ala	Glu	Ser	
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Ala	Ser	Glu	Cys	Leu	Pro	Cys	Asp	Cys	Asn	Gly	Arg	Ser	Gln	Glu	Cys	
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Tyr	Phe	Asp	Pro	Glu	Leu	Tyr	Arg	Ser	Thr	Gly	His	Gly	Gly	His	Cys	
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Thr	Asn	Cys	Arg	Asp	Asn	Thr	Asp	Gly	Ala	Lys	Cys	Glu	Arg	Cys	Arg	
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gag	aat	ttc	ttc	cgc	ctg	ggg	aac	act	gaa	gcc	tgc	tct	ccg	tgc	cac	1383
Glu	Asn	Phe	Phe	Arg	Leu	Gly	Asn	Thr	Glu	Ala	Cys	Ser	Pro	Cys	His	
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tgc	agc	cct	gtt	ggg	tct	ctc	agc	aca	cag	tgt	gac	agt	tac	ggc	aga	1431
Cys	Ser	Pro	Val	Gly	Ser	Leu	Ser	Thr	Gln	Cys	Asp	Ser	Tyr	Gly	Arg	
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Cys	Ser	Cys	Lys	Pro	Gly	Val	Met	Gly	Asp	Lys	Cys	Asp	Arg	Cys	Gln	
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Pro	Gly	Phe	His	Ser	Leu	Thr	Glu	Ala	Gly	Cys	Arg	Pro	Cys	Ser	Cys	
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Phe	Cys	Phe	Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	
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Leu Gly Ser Asn Gly Pro Val Arg Leu Cys Arg Pro Cys Gln Cys Asn	
815 820 825	
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Asp Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly	
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Cys Lys Glu Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp	
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Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val Thr
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Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His Leu
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Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp Thr
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Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile Thr Tyr
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Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala Ile Tyr
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Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe Phe Asn	
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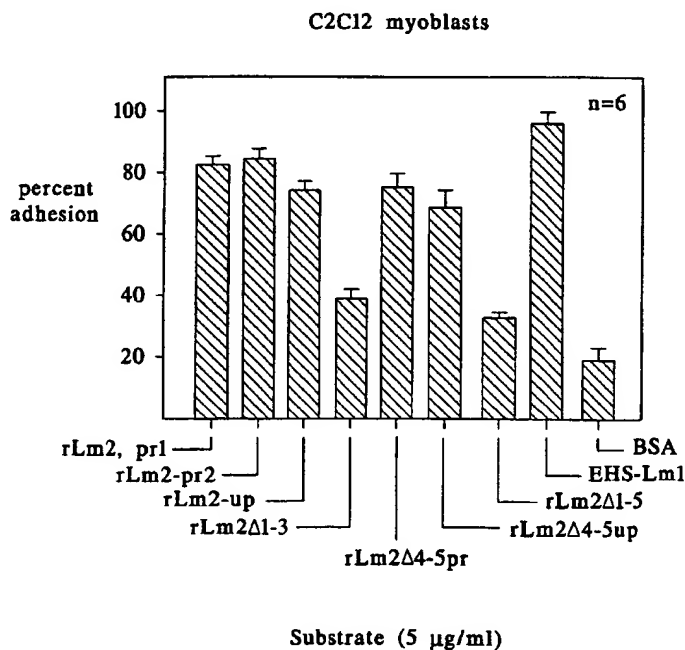
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[Continued on next page]

(54) Title: LAMININ 2 AND METHODS FOR ITS USE



(57) Abstract: The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.



Published:

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A. CLASSIFICATION OF SUBJECT MATTER

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A61P9/00 A61P21/00 A61P25/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08628 A (JOLLA CANCER RES FOUND) 30 March 1995 (1995-03-30)	30-33
Y	SeqIdNo.4: 100.0% identity in 3098 aa overlap with SeqIdNo.2 / 99.8% identity in 9535nt overlap with SeqIdNo.1 claims 14-16,18,30,33; figure 6	16-18, 22-24, 28,29
X	UTANI A ET AL: "A specific sequence of the laminin alpha 2 chain critical for the initiation of heterotrimer assembly" JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 270, no. 7, 17 February 1995 (1995-02-17), pages 3292-3298, XP002153607	1-15
Y	figure 4	16-18, 22-24, 28,29

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☒ Patent family members are listed in annex.

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *G* document member of the same patent family

Date of the actual completion of the international search

8 December 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/11378

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TALTS J ET AL: "Structural analysis and proteolytic processing of recombinant G domain of mouse laminin alpha2 chain" FEBS LETTERS., vol. 426, no. 1, 10 April 1998 (1998-04-10), pages 71-76, XP002153608 figure 1B	30-33
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FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-29 (all totally) and 34 (partially)

Laminin 2, materials and methods for its recombinant production, and applications thereof.

2. Claims: 30-33 (all totally) and 34 (partially)

Laminin alpha 2 chain consisting of the sequence SeqIdNo.1-2, and application thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/11378

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